CANNABIS IN NEUROINFLAMMATORY DISEASES

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Thairath หมอดื้อ

ยาสมองเสื่อม - พาร์กินสัน ?

- มีบทบาทตรงระดับใดที่ช่วยรักษาโรค?
- เป็นเพียงบรรเทาอาการ กระตุ้นสมองที่ยังทำงานได้ที่มีน้อยอยู่แล้ว ให้ทำงานหนัก
- มีผลข้างเคียง

Is it really useful for screening?

Screening, drug sale promotion?

Annals of Internal Medicine | CLINICAL GUIDELINE

Screening for Cognitive Impairment in Older Adults: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for dementia.

Methods: The USPSTF reviewed the evidence on the benefits, harms, and sensitivity and specificity of screening instruments for cognitive impairment in older adults and the benefits and harms of commonly used treatment and management options for older adults with mild cognitive impairment or early dementia and their caregivers.

Population: This recommendation applies to universal screening with formal screening instruments in community-dwelling adults in the general primary care population who are older than 65 years and have no signs or symptoms of cognitive impairment.

Recommendation: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment. (I statement)

Ann Intern Med. www.annals.org

For author affiliation, see end of text.
* For a list of USPSTF members, see the **Appendix** (available at www.annals.org).

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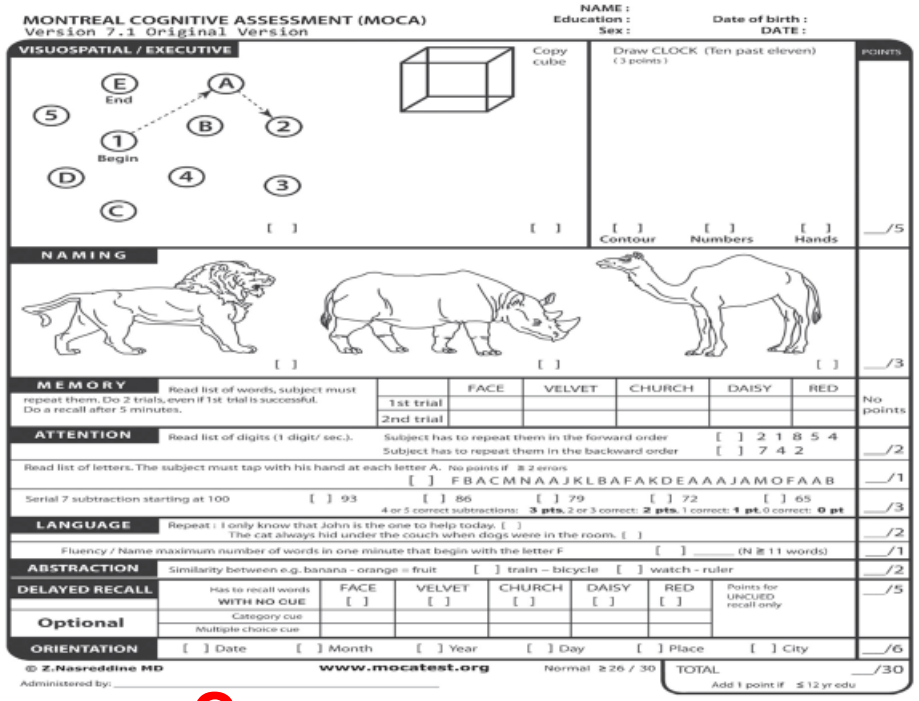


ยาขณะนี้ไม่ช่วย เกิดผลข้างเคียง การ screen?

Treatment of mild to moderate dementia with several drug therapies and nonpharmacologic interventions results in small improvements in measures of cognitive function and caregiver outcomes, but the clinical significance of these improvements is uncertain. The USPSTF found no published evidence on the effect of screening on decision making or planning by patients, clinicians, or caregivers. Evidence on the harms of screening and nonpharmacologic interventions is inadequate. The USPSTF found adequate evidence that AChEIs are associated with adverse effects, some of which are serious. Overall, the USPSTF was unable to estimate the balance of benefits and harms of screening for cognitive impairment.

Administration–approved drugs for dementia. Given that current therapies for dementia do not seem to affect the long-term progression of mild to moderate cognitive impairment, the hope is for effective interventions that can help patients and caregivers prepare for dealing with dementia symptoms.

Levodopa: no effect on PD progression (BUT dose matters)

วารสารนิวอิงแลนด์ ที่ 24 มกราคม 2019 รายงานว่ายาพาร์กินสัน levodopa 100 carbidopa 25 ให้เร็วหรือให้ช้าจะไม่มีผลในการชะลอโรคหรือเร่งให้โรคไปเร็ว ซึ่งไม่เหมือนกับรายงานก่อนหน้านี้ที่แสดงว่ายาเร่งให้สมองส่วนที่สร้างสารสื่อประสาทตายเร็วขึ้น แม้ดูเหมือนว่าจะทำให้โรคช้าลงซึ่งดูไม่เป็นเหตุเป็นผลซึ่งกันและกัน
สำหรับรายงานนี้
ประการสำคัญที่ต้องทำความเข้าใจ
1- ปริมาณยาที่ให้อยู่ในขนาดน้อยตามที่ ได้มีคำแนะนำก่อนหน้านี้ว่าแต่ละครั้งไม่ควรเกิน 125 มก
2-ปริมาณต่อวัน = สามครั้ง
3-เป็นการติดตาม 80 สัปดาห์กลุ่มแรกให้ตั้งแต่ต้นกลุ่มที่สองให้หลังสัปดาห์ที่ 40
4-ในประเทศไทยมีการให้ยาเต็มเหนี่ยวทุกประเภทที่มีในขนาดสูงรวมทั้งกลุ่มที่ทำให้ยาค้างอยู่ได้ในสมองนาน มีทั้งยาน้ำ ยาแปะ รวมทั้งยาที่คิดว่าจะช่วยชะลอโรคและช่วยสั่น
แต่สิ่งที่เห็นคือคนไข้ไปเร็วมากภายในช่วงสองปีสามปีกลายเป็นช่วยตัวเองไม่ได้และมีผลข้างเคียงของยามากมาย
ทั้งนี้รายงานจากยุโรปที่มีก่อนหน้านั้นแสดงว่าถ้าใช้ยาในขณะวันละไม่เกิน 650 ถึง 900 มิลลิกรัมต่อวันยังอยู่ได้ 25 ถึง 30 ปี

ดังนั้นสิ่งที่ควรปฏิบัติคือ
ให้ยาเมื่อจำเป็นต้องให้ ให้ยาในขนาดน้อยที่สุดที่ช่วยบรรเทาอาการคนไข้

ตระหนักอยู่เสมอว่ายาพากินสัน นั้นเช่นเดียวกับยาในโรคสมองเสื่อมเป็นยาบรรเทาอาการไม่ใช่ยารักษาโรคหรือชะลอโรคการให้มากเกินไปมีผลข้างเคียงแน่นอนและเกิดปัญหาเสียเงินโดยไม่จำเป็นเดือนละ 20,000 ถึง 30,000 บาท

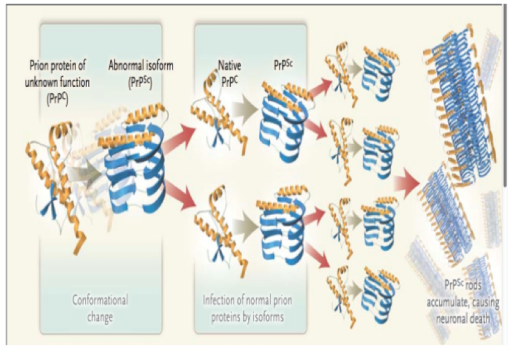
No Effect of Levodopa on Parkinson's Progression

SCOPE

- **CURRENT TREATMENT: DOES IT REALLY WORK?**
- **WHY?**

WHAT WE NOW KNOW…….

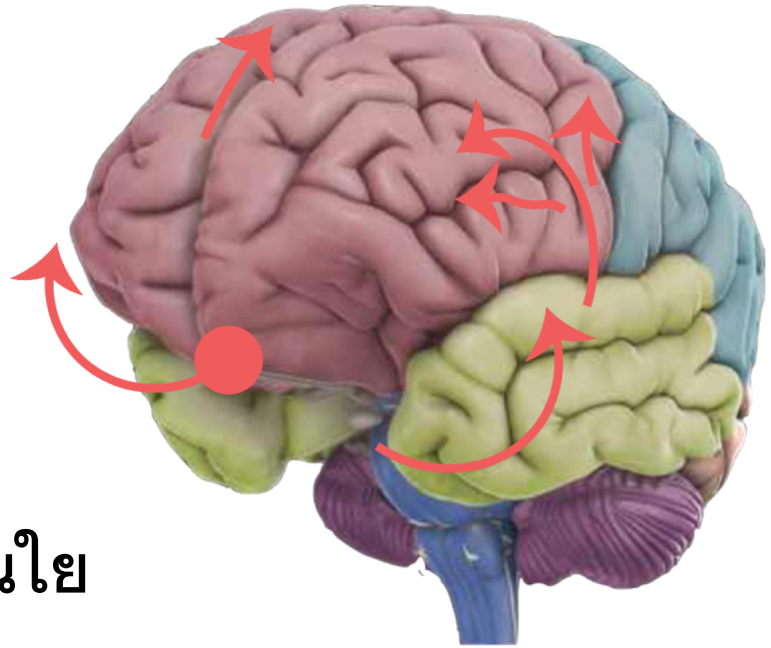
- **Misfolded protein: functional-structural disorder**
- **How it happens**
- **Intrinsic-extrinsic**
- **Cascades from the beginning: food/toxicants**
- **How we can get it**
- **Gut-nerve transport**
- **Propagation or route of spread**



NEUROINFLAMMATORY DISEASES

Outside in/ Inside out

อัลไซเมอร์



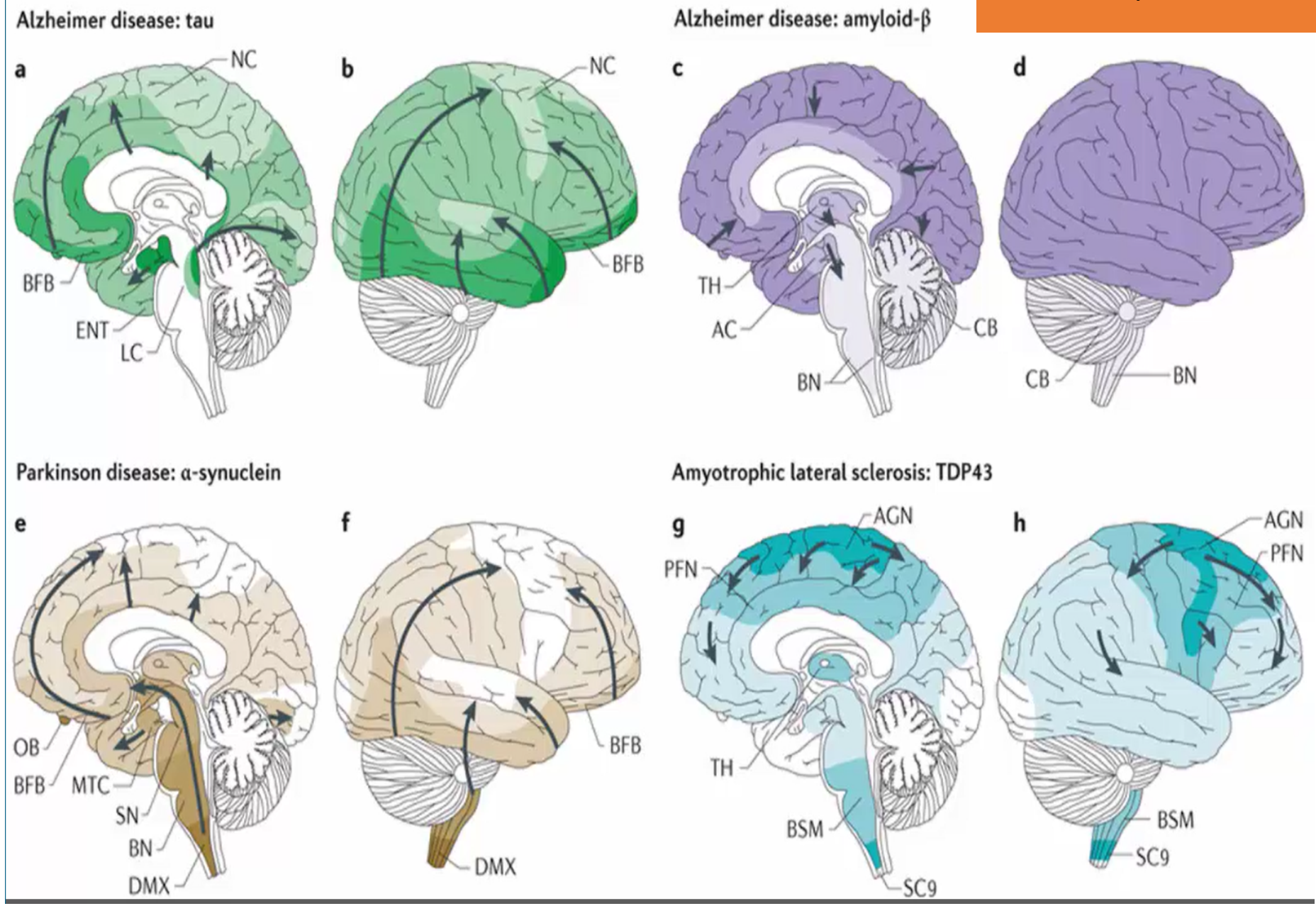
สารพิษ

กระจายตามเส้นใย

ตามระบบระเบียบ

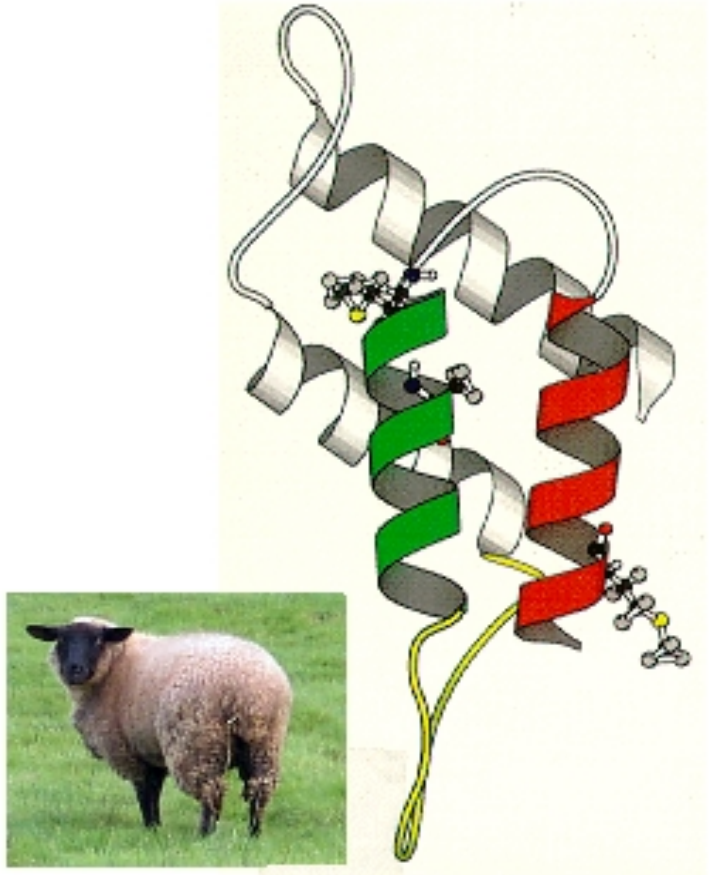
แบบแผน

misfolded protein

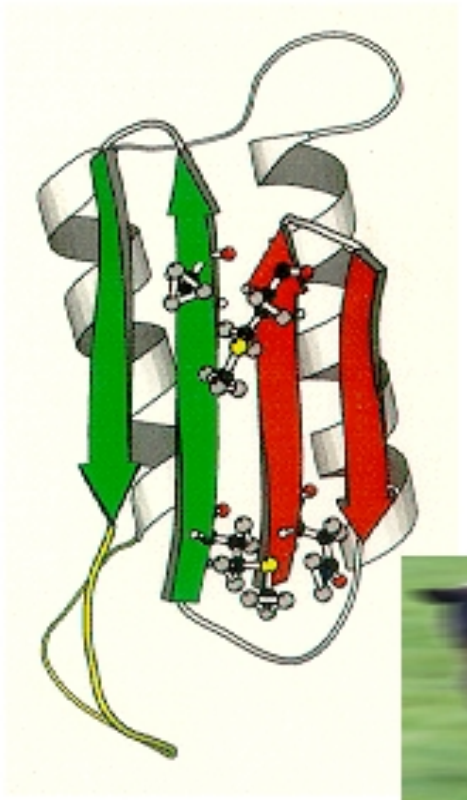


Nature of Prions

Prion normal : PrP



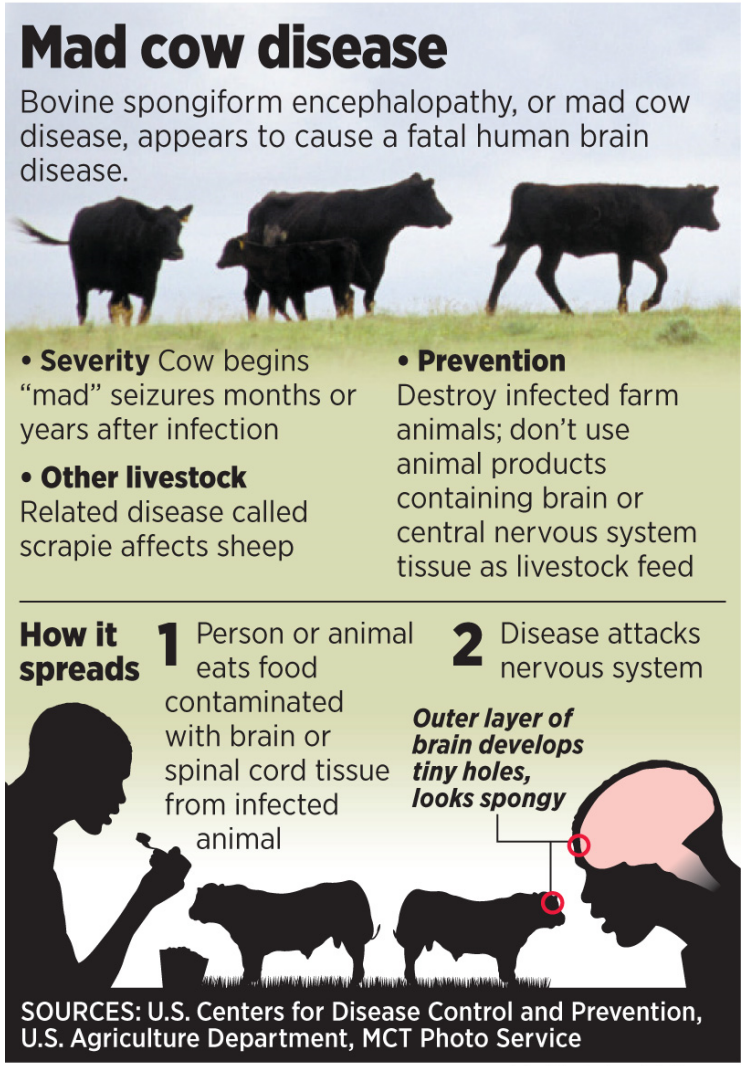
Prion anormal : PrPsc



GUT BRAIN AXIS

- The earliest evidence that the gut might be involved in Parkinson's emerged more than 200 years ago.
- In 1817, the English surgeon James Parkinson reported that some patients with a condition he termed "shaking palsy" experienced constipation. In one of the six cases he described, treating the gastrointestinal complaints appeared to alleviate the movement-related problems associated with the disease.

MAD COW DISEASE



McClatchy-Tribune

Why crucial?

Oral route
Port of entry
similar to BSE
and vCJD

ครึ่งๆ

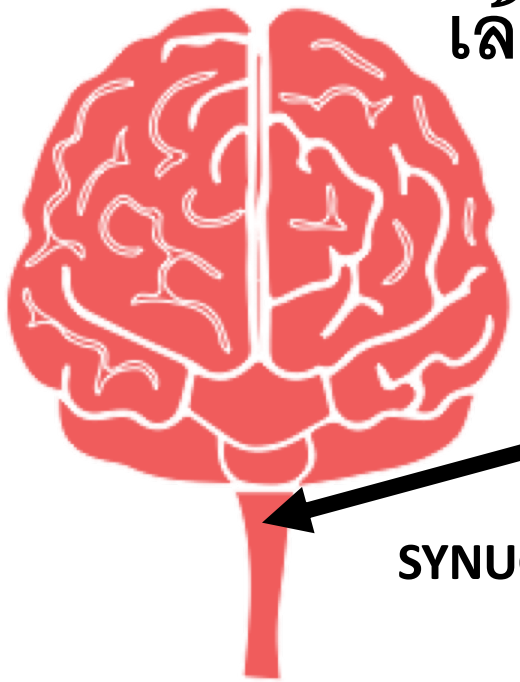
ชะตาขาด — ชะตาดี

ดวงชะตา

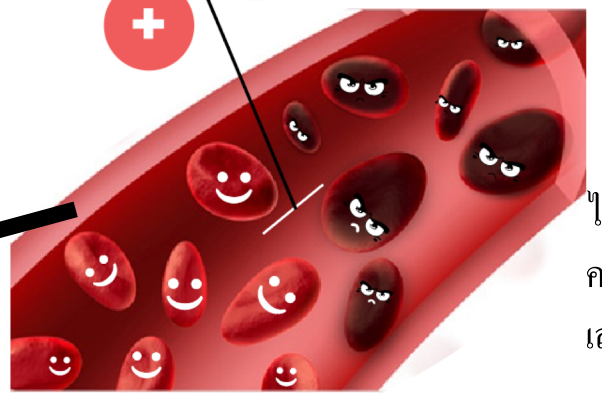
อักเสบภายใน

อ้วน ความดัน บุหรี่

เส้นเลือด



เส้นประสาท



เนื้อแดง

อาหาร

ไข่แดง

คาร์นิทีน

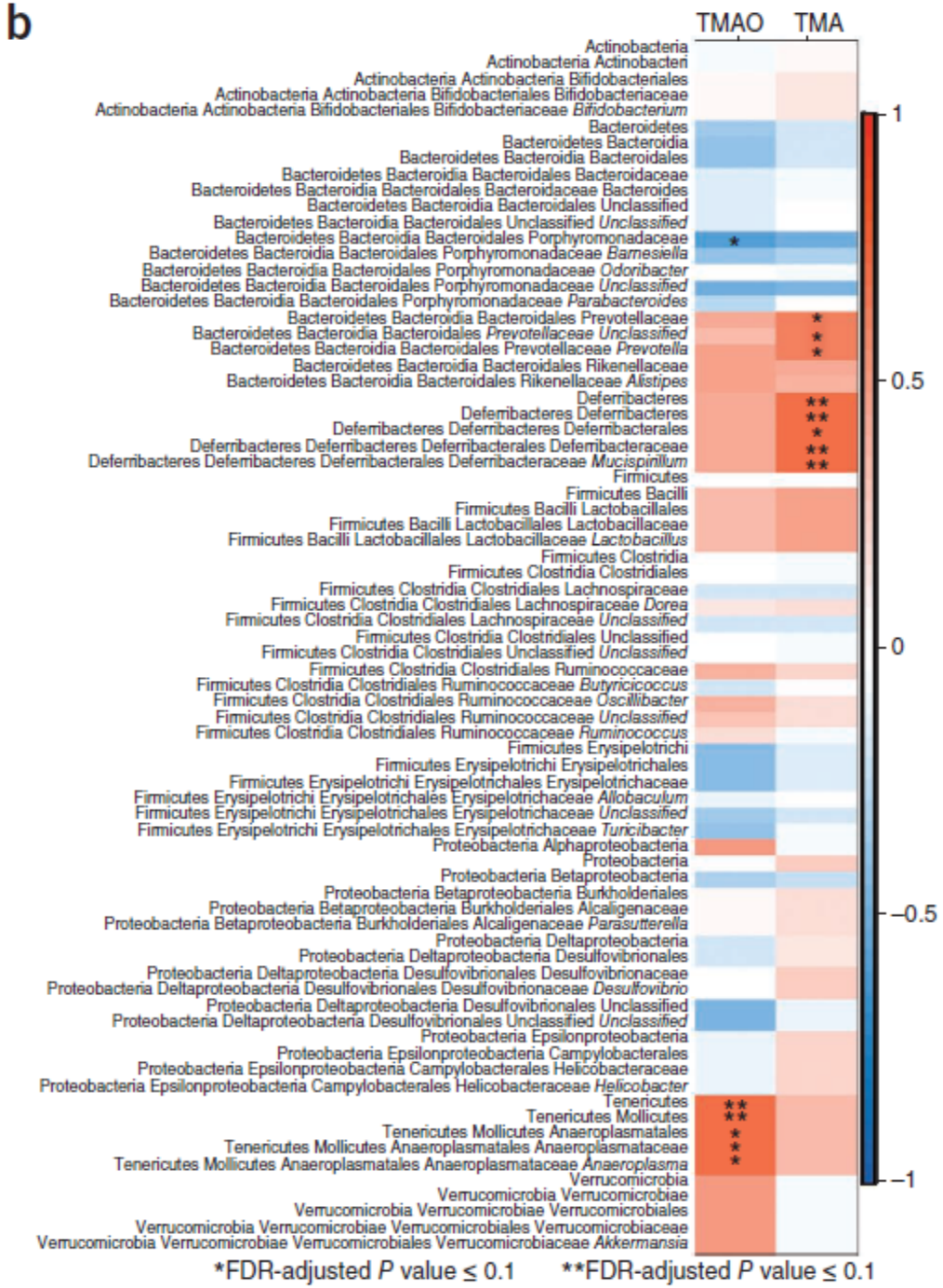
เลซิติน

SYNUCLEIN

อักเสบภายนอก

มลพิษ สารเคมี อาหาร

PARKINSON'S DISEASE



Gut microbiome

IL-17….
NF-κB-mediated “inflammation amplifier”

IFN-gamma/TGF-beta-1 and the TH1/TH2 balance correspond to the M1/M2 and the balance of tissue destruction
(i.e., excessive nitric oxide and related cytotoxic compounds)/ tissue regeneration modality (i.e., arginase-mediated production of polyamines for DNA repair and L-proline and ornithine for cell and tissue repair)

M1 destructive
M2 reparative

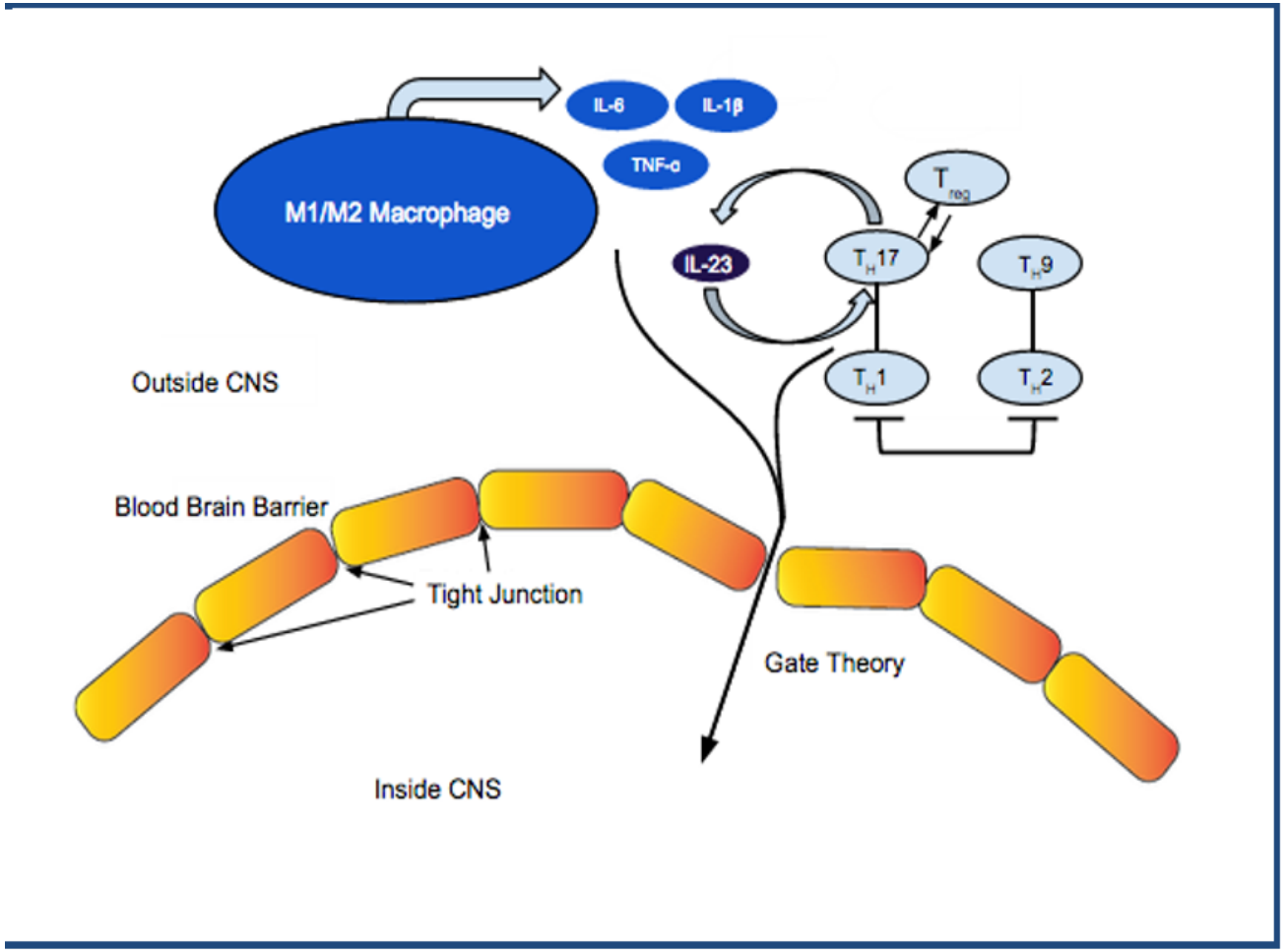


Figure 1: The TH17/TH9 BBB Gateway

Also TH17/TH10 gateway

nature COMMUNICATIONS

ARTICLE

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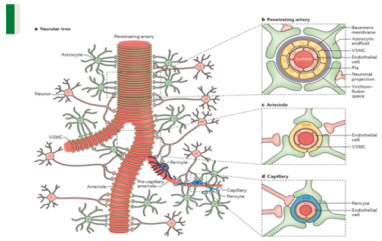
DOI: 10.1038/ncomms11934 OPEN

Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis

Y. Iturria-Medina[1,2], R.C. Sotero[3], P.J. Toussaint[1,2], J.M. Mateos-Pérez[1,2], A.C. Evans[1,2] & The Alzheimer's Disease Neuroimaging Initiative[†]



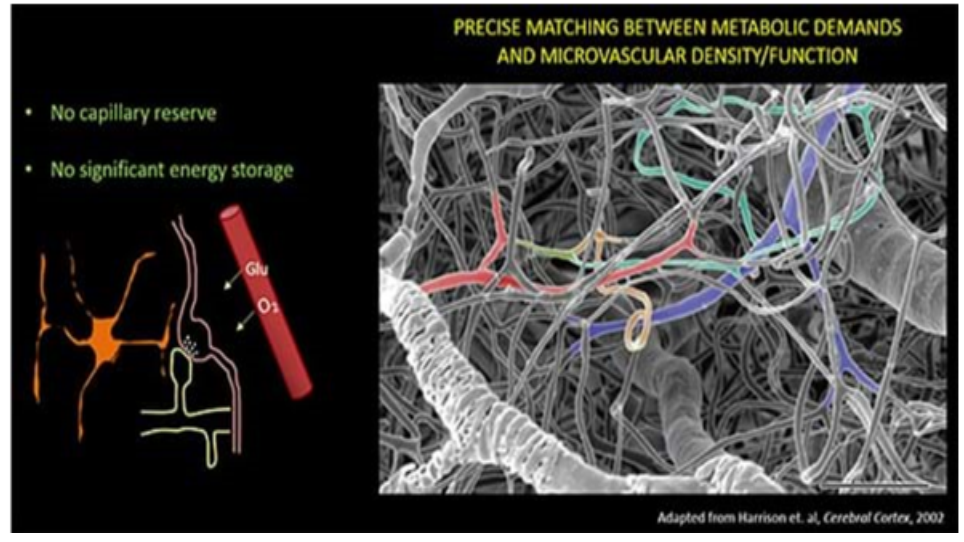
Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease

Kassandra Kisler, Amy R. Nelson*, Axel Montagne* and Berislav V. Zlokovic*

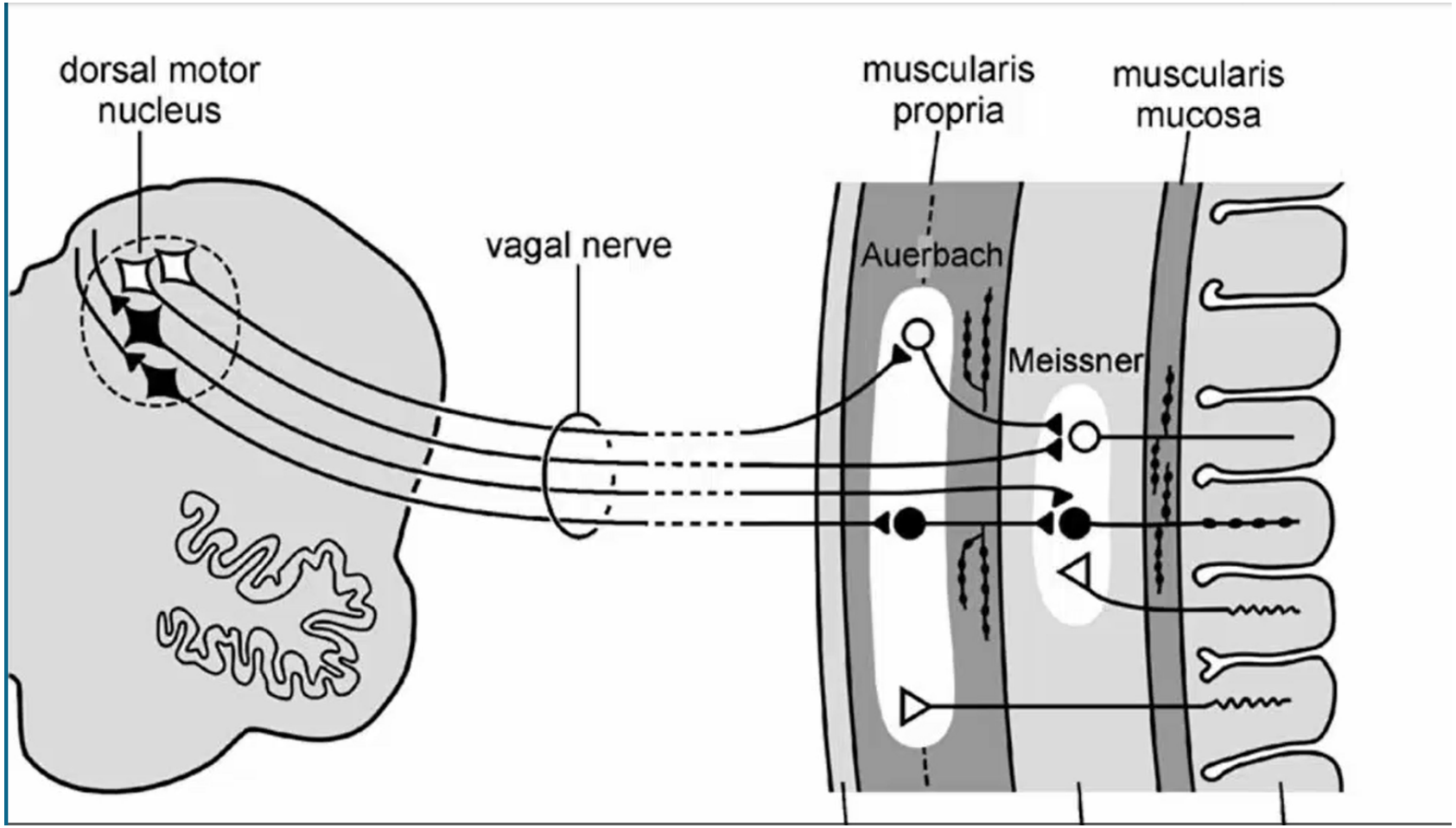
Abstract | Cerebral blood flow (CBF) regulation is essential for normal brain function. The mammalian brain has evolved a unique mechanism for CBF control known as neurovascular coupling. This mechanism ensures a rapid increase in the rate of CBF and oxygen delivery to activated brain structures. The neurovascular unit is composed of astrocytes, mural vascular smooth muscle cells and pericytes, and endothelia, and regulates neurovascular coupling. This Review article examines the cellular and molecular mechanisms within the neurovascular unit that contribute to CBF control, and neurovascular dysfunction in neurodegenerative disorders such as Alzheimer disease.

Blood flow in the brain must be precisely regulated because the brain does not store energy and can't recruit new capillaries when more oxygen is needed. (Image courtesy of Jaime Grutzendler)

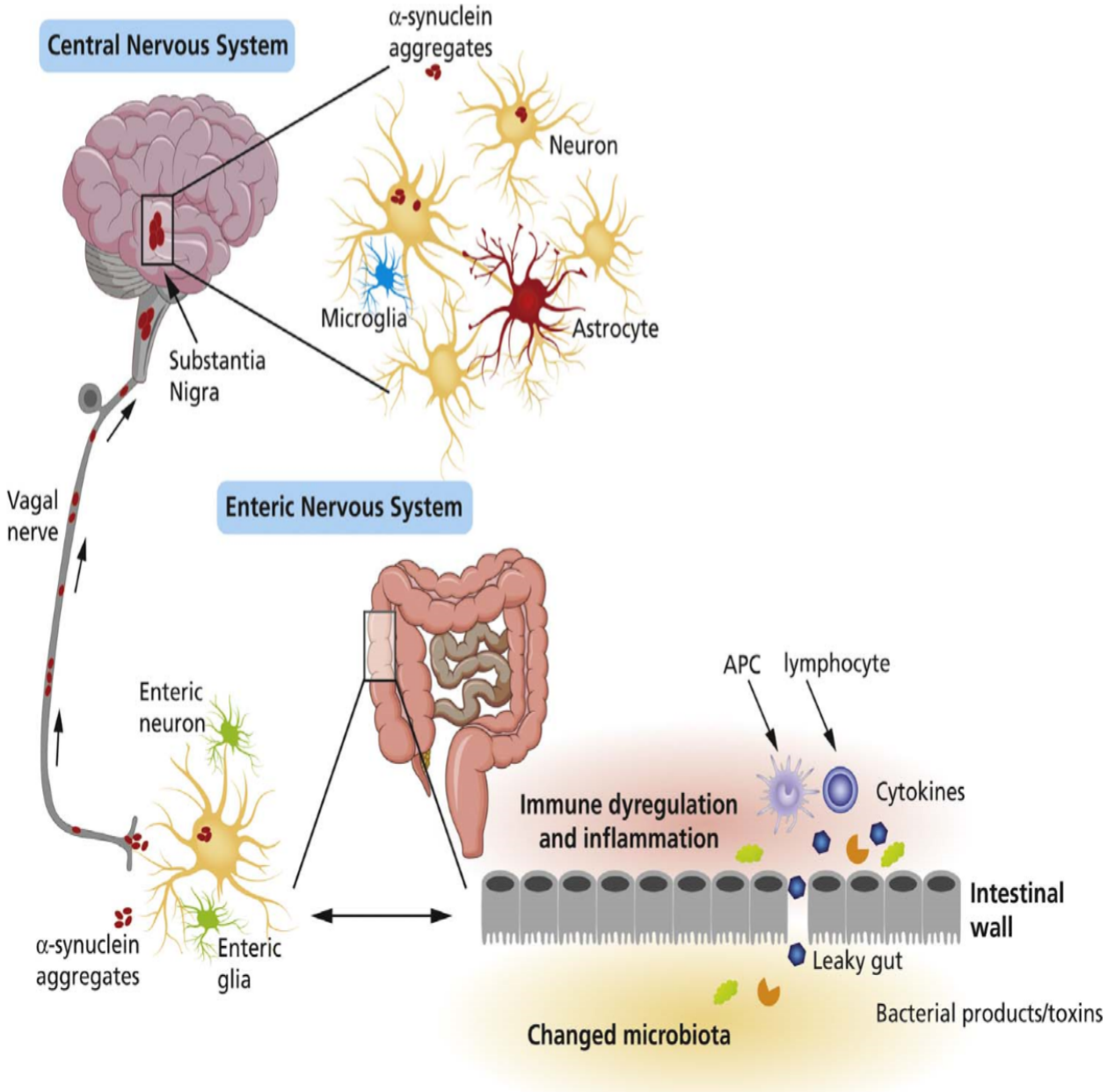
nyas2017

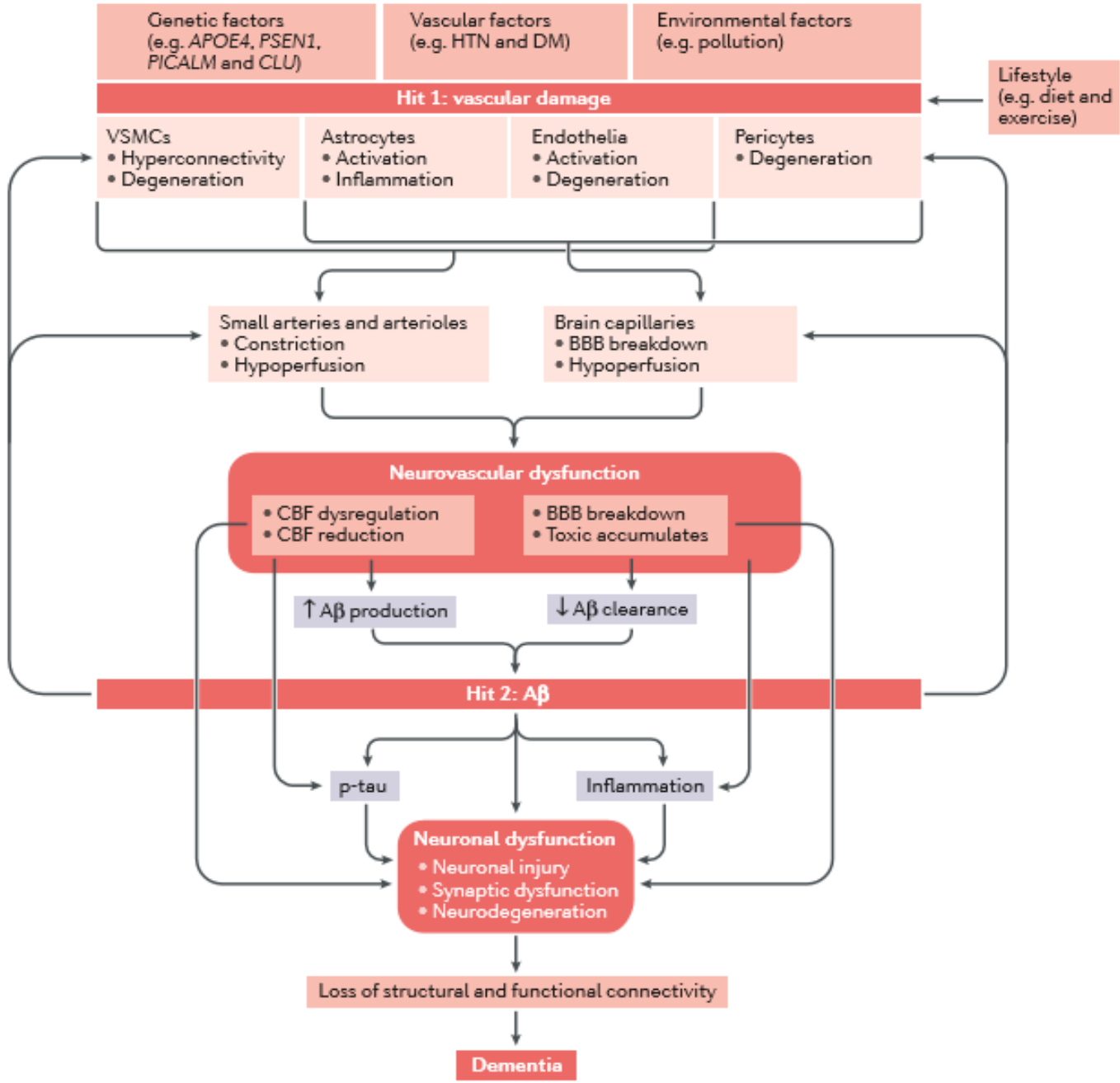


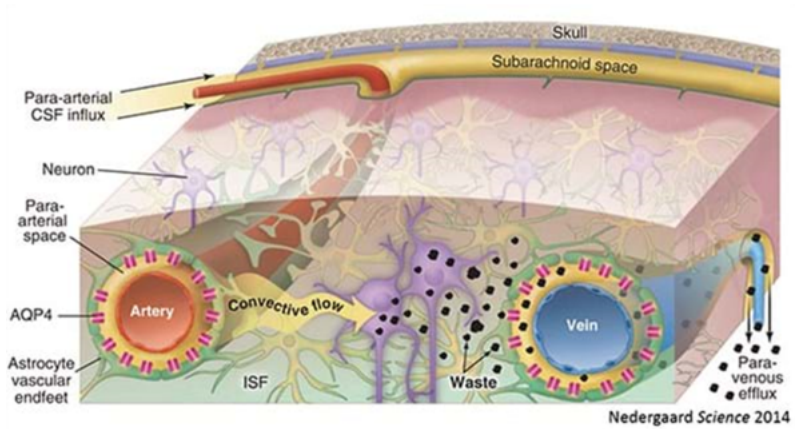
Over production of synuclein but in "misfolded form" and TRANSPORT route



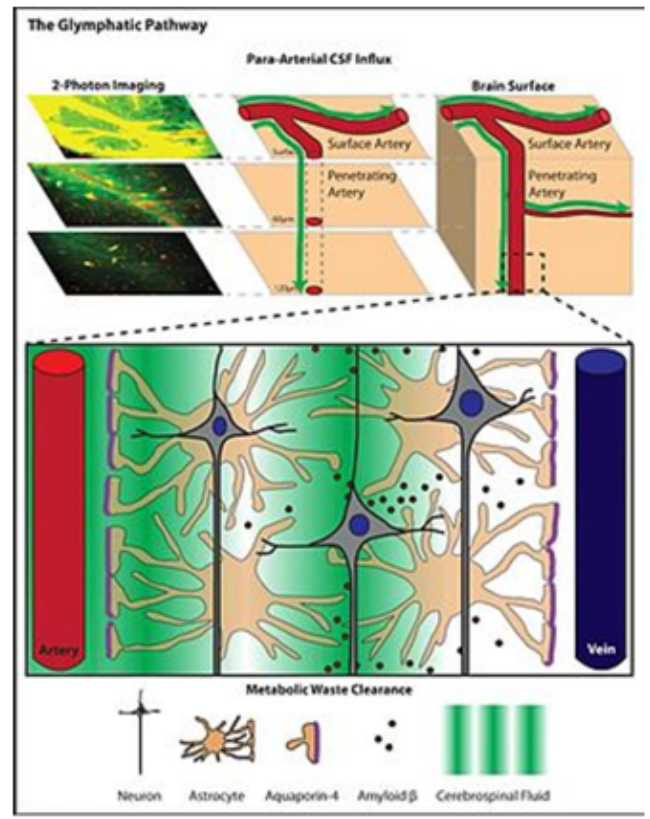
NY ACADEMY OF SCIENCE


Central Nervous System
α-synuclein aggregates
Neuron
Microglia
Astrocyte
Substantia Nigra
Vagal nerve
Enteric Nervous System
Enteric neuron
α-synuclein aggregates
Enteric glia
APC
lymphocyte
Cytokines
Immune dyregulation and inflammation
Intestinal wall
Leaky gut
Bacterial products/toxins
Changed microbiota


Genetic factors (e.g. APOE4, PSEN1, PICALM and CLU)
Vascular factors (e.g. HTN and DM)
Environmental factors (e.g. pollution)
Lifestyle (e.g. diet and exercise)
Hit 1: vascular damage
VSMCs
• Hyperconnectivity
• Degeneration
Astrocytes
• Activation
• Inflammation
Endothelia
• Activation
• Degeneration
Pericytes
• Degeneration
Small arteries and arterioles
• Constriction
• Hypoperfusion
Brain capillaries
• BBB breakdown
• Hypoperfusion
Neurovascular dysfunction
• CBF dysregulation
• CBF reduction
• BBB breakdown
• Toxic accumulates
↑ Aβ production
↓ Aβ clearance
Hit 2: Aβ
p-tau
Inflammation
Neuronal dysfunction
• Neuronal injury
• Synaptic dysfunction
• Neurodegeneration
Loss of structural and functional connectivity
Dementia



The recently-discovered glymphatic system clears cellular



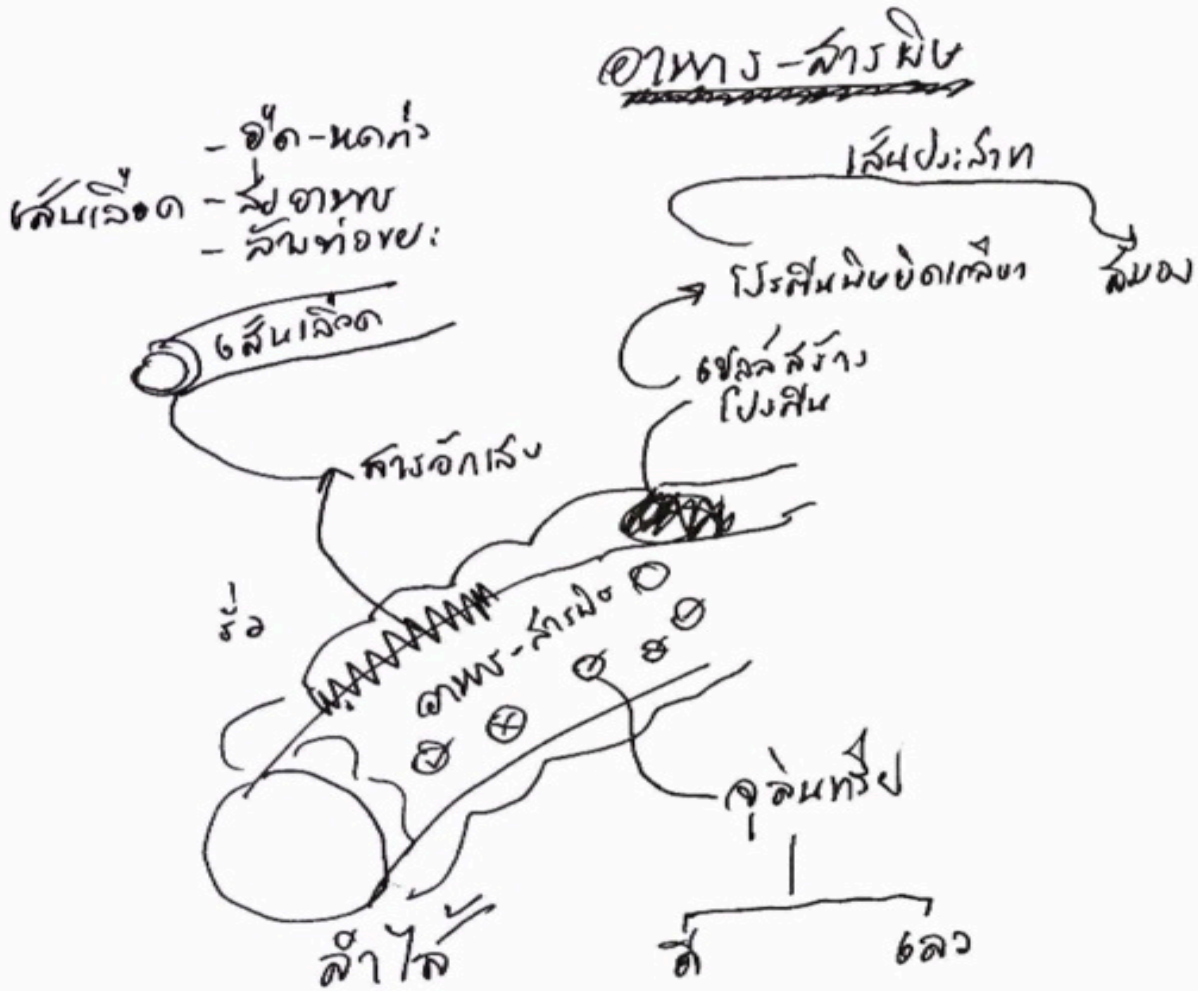
Review

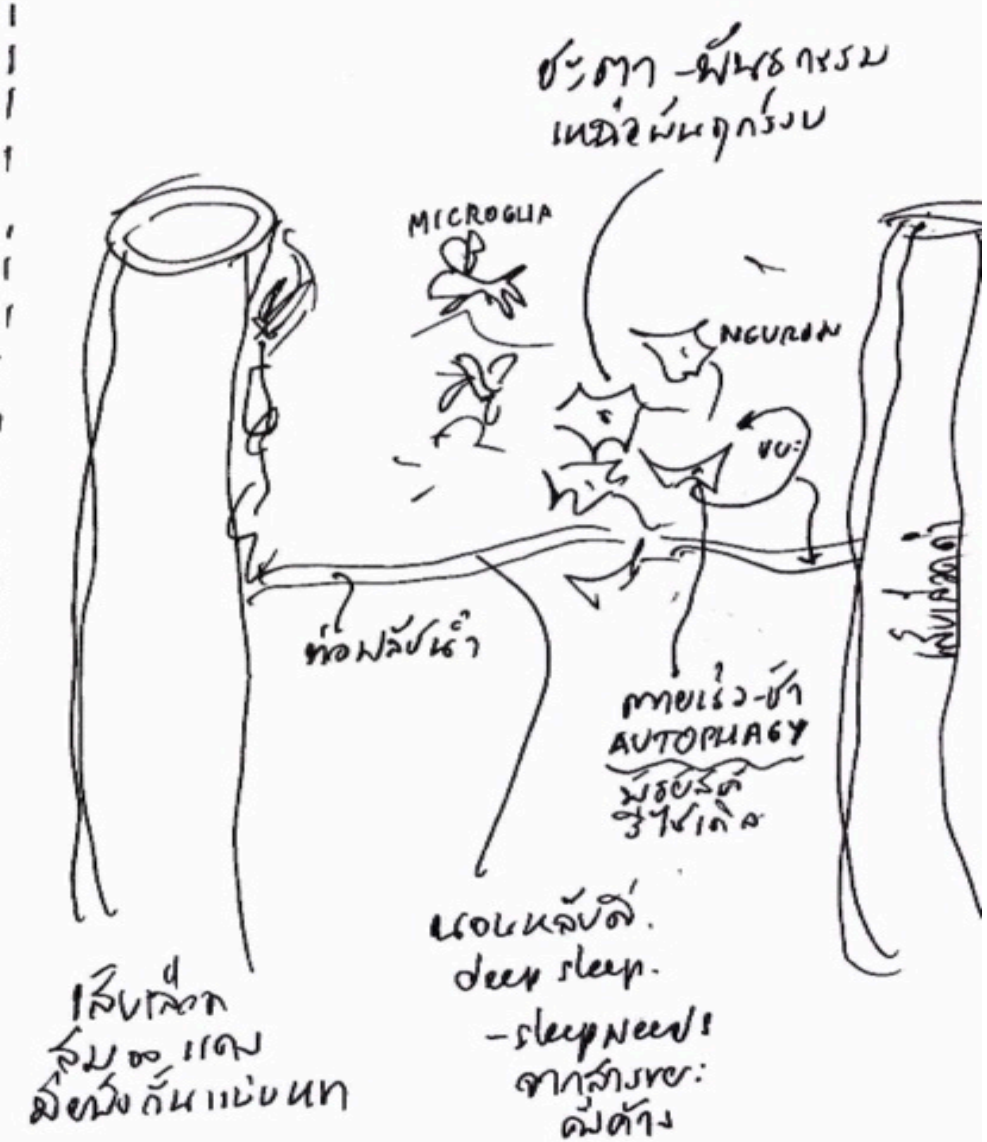
The Glymphatic Pathway: Waste Removal from the CNS via Cerebrospinal Fluid Transport

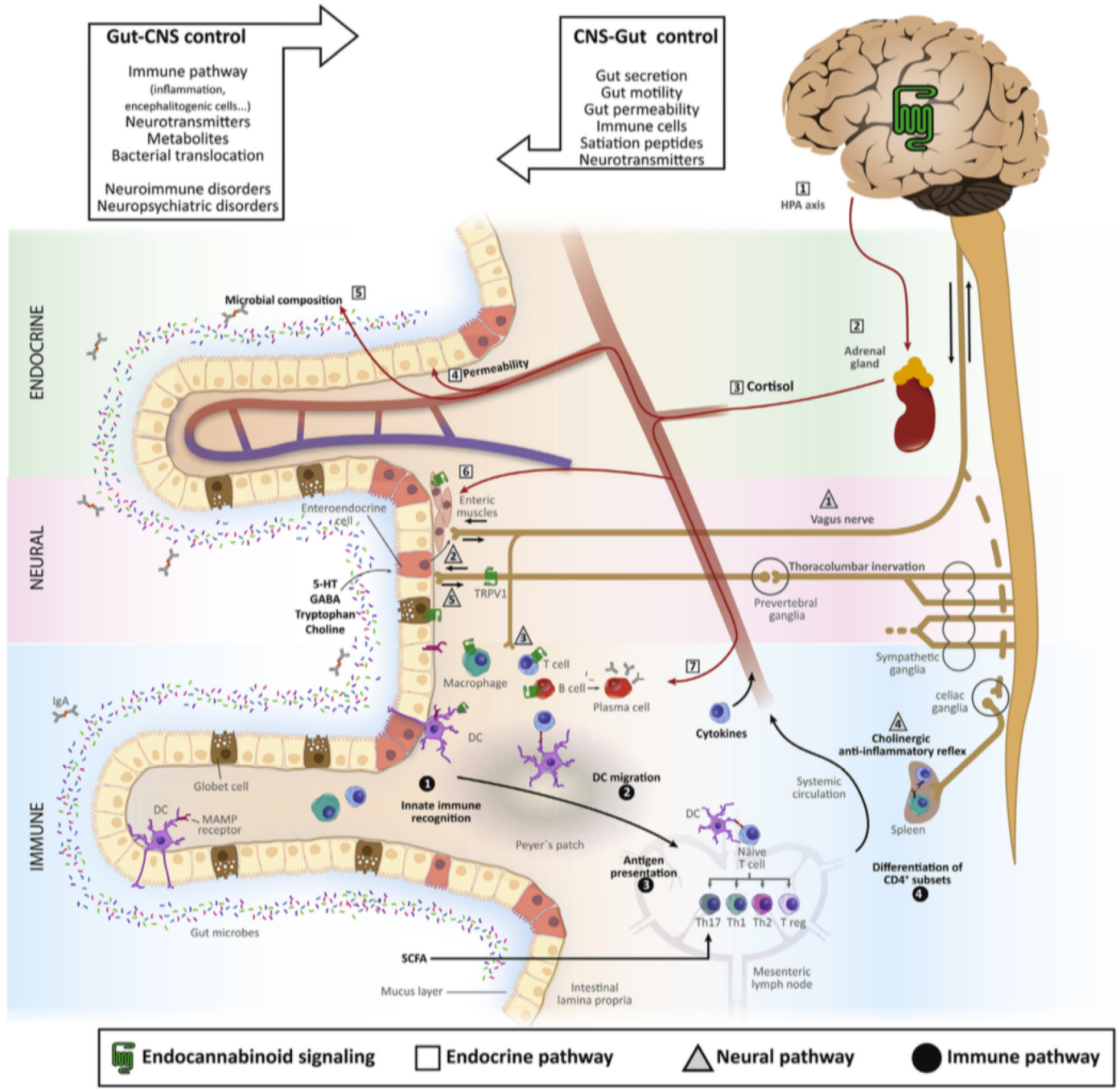
The Neuroscientist
1–12

DOI: 10.1177/1073858417691030
journals.sagepub.com/home/nro
SAGE

Helene Benveniste[1], Hedok Lee[1], and Nora D. Volkow[2]

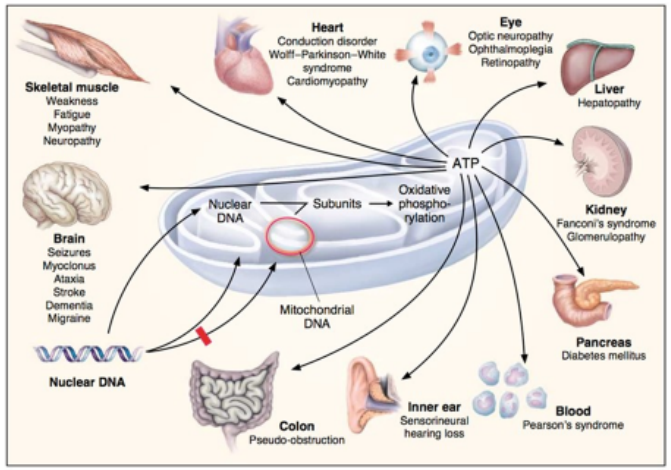

อาหาร-สารพิษ
- อุจ-หดก่ง
เส้นเลือด - ลู่อาหาร
- ลำไส้ขยะ
เส้นประสาท
สมอง
โปรตีนพิษยึดเกลียว
เส้นเลือด
เซลล์สร้างโปรตีน
สารอักเสง
ร้อ
อาหาร-ลำไส้
อุจจาระ
ลำไส้
ดี
เลว

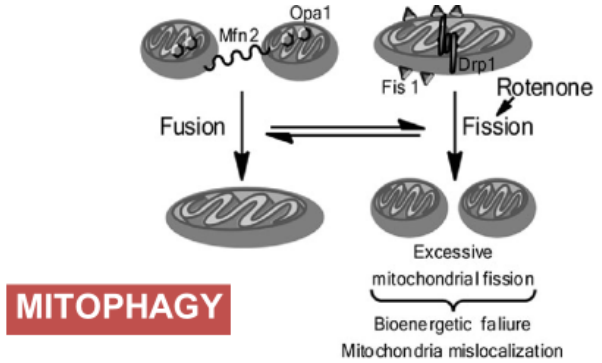

ชะตา-พันธุกรรม
เหมือนกันทุกประการ
MICROGLIA
NEURON
ขยะ
ท่อน้ำทิ้ง
ตายเร็ว-ช้า
AUTOPHAGY
มีธรรมชาติ
ที่ไม่เหมือน
เส้นเลือด
สมอง แดง
มีหนังกันแบ่งหน้า
นอนหลับลึก
deep sleep
-sleepNeed
ตามสภาพ
ผู้ต้าง


Gut-CNS control
Immune pathway
(inflammation,
encephalitogenic cells...)
Neurotransmitters
Metabolites
Bacterial translocation
Neuroimmune disorders
Neuropsychiatric disorders
CNS-Gut control
Gut secretion
Gut motility
Gut permeability
Immune cells
Satiation peptides
Neurotransmitters
ENDOCRINE
NEURAL
IMMUNE
1 HPA axis
2 Adrenal gland
3 Cortisol
4 Permeability
5 Microbial composition
6 Enteric muscles
1 Vagus nerve
2
5 TRPV1
Thoracolumbar inervation
Prevertebral ganglia
Sympathetic ganglia
celiac ganglia
4 Cholinergic anti-inflammatory reflex
Spleen
Enteroendocrine cell
5-HT
GABA
Tryptophan
Choline
3
T cell
B cell
Plasma cell
Macrophage
7
Cytokines
IgA
DC
Globet cell
DC
MAMP receptor
1 Innate immune recognition
DC migration 2
Systemic circulation
Peyer´s patch
DC
Naïve T cell
Antigen presentation 3
Differentiation of CD4+ subsets 4
Th17 Th1 Th2 T reg
Gut microbes
SCFA
Mucus layer
Intestinal lamina propria
Mesenteric lymph node
Endocannabinoid signaling
Endocrine pathway
Neural pathway
Immune pathway

ENERGY CRISIS/BIO-ENERGETIC FAILURE

https://www.nyas.org/ebriefings/2018/mitochondria-and-medicine/?tab=session%20ii:%20understanding%20the%20importance%20of%20mitochondria%20from%20cell%20biology%20to%20human%20health





MITOPHAGY

FIG. 1. Dysregulated mitochondrial dynamics in Parkinson's disease toxin models. Dynamic balance between mitochondrial fission and fusion is required for normal cell homeostasis and function. Mitochondrial fusion occurs when mitofusion proteins (Mfn) link the outer mitochondrial membranes of two separate mitochondria, and the protein Opa1, which resides in the inner mitochondrial membrane, facilitates fusion of the inner mitochondrial membranes, resulting in the fusion of one mitochondria from two. Mitochondrial fission occurs when the fission protein Fis1 demarks the outer mitochondrial membrane, and by interaction with Drp1, promotes the fission of a single mitochondria into two individual mitochondria. Excessive mitochondria fusion is detrimental to cell survival, and rotenone promotes aberrant mitochondrial fusion.

ANTIOXIDANTS & REDOX SIGNALING
Volume 16, Number 9, 2012

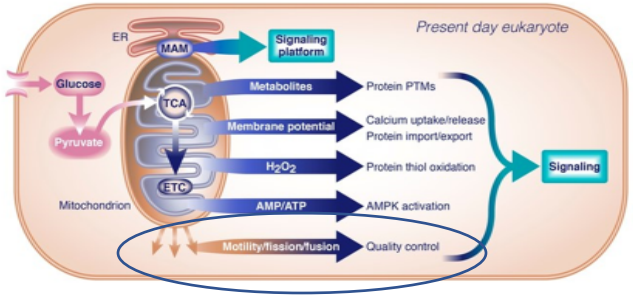
DOI: 10.1089/ars.2011.4033

FORUM REVIEW ARTICLE

Toxin Models of Mitochondrial Dysfunction in Parkinson's Disease

Terina N. Martinez and J. Timothy Greenamyre

Mitochondria as signaling



Chandel, Cell Metabolism 2015

Mighty chondria
Autophagy
NYAS 2017

Science. 2012 Aug 31; 337(6098): 1062–1065.

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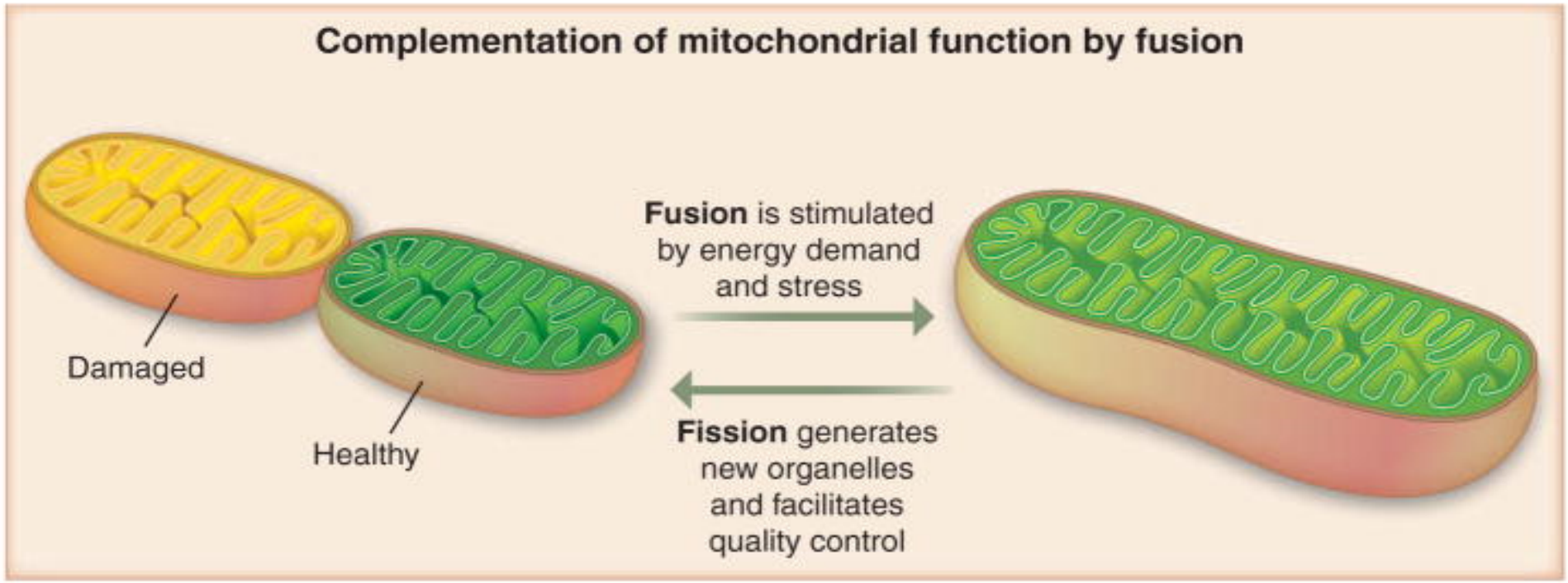
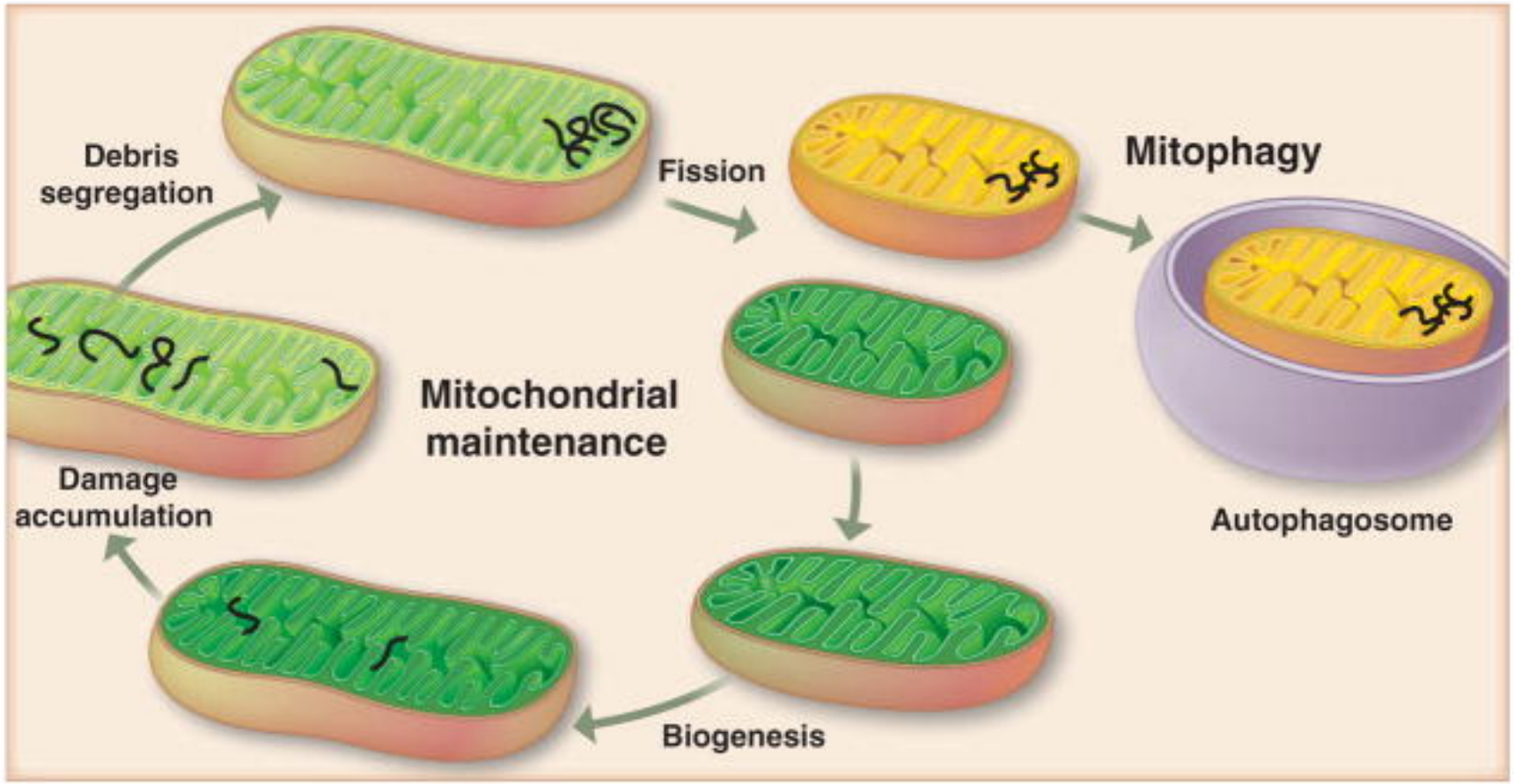
Mitochondrial Fission, Fusion, and Stress

Richard J. Youle1,* and Alexander M. van der Bliek2,*



Fusion rescues stress by allowing functional mitochondria (green) to complement dysfunctional mitochondria (yellow) by diffusion and sharing of components between organelles. Stress-induced hyperfusion yields maximal potential (light green), whereas under relaxed conditions cells are able to segregate the damaged (yellow) ones.

Autophagy could purify the cellular pool of mitochondria if debris is aggregated and segregated by fission in a subset of mitochondria. If deleterious components (black fibers) are asymmetrically distributed or aggregated, fission could lead to cleansing of daughter mitochondrion (green) by preventing fusion and inducing mitophagy of the impaired ones (yellow).



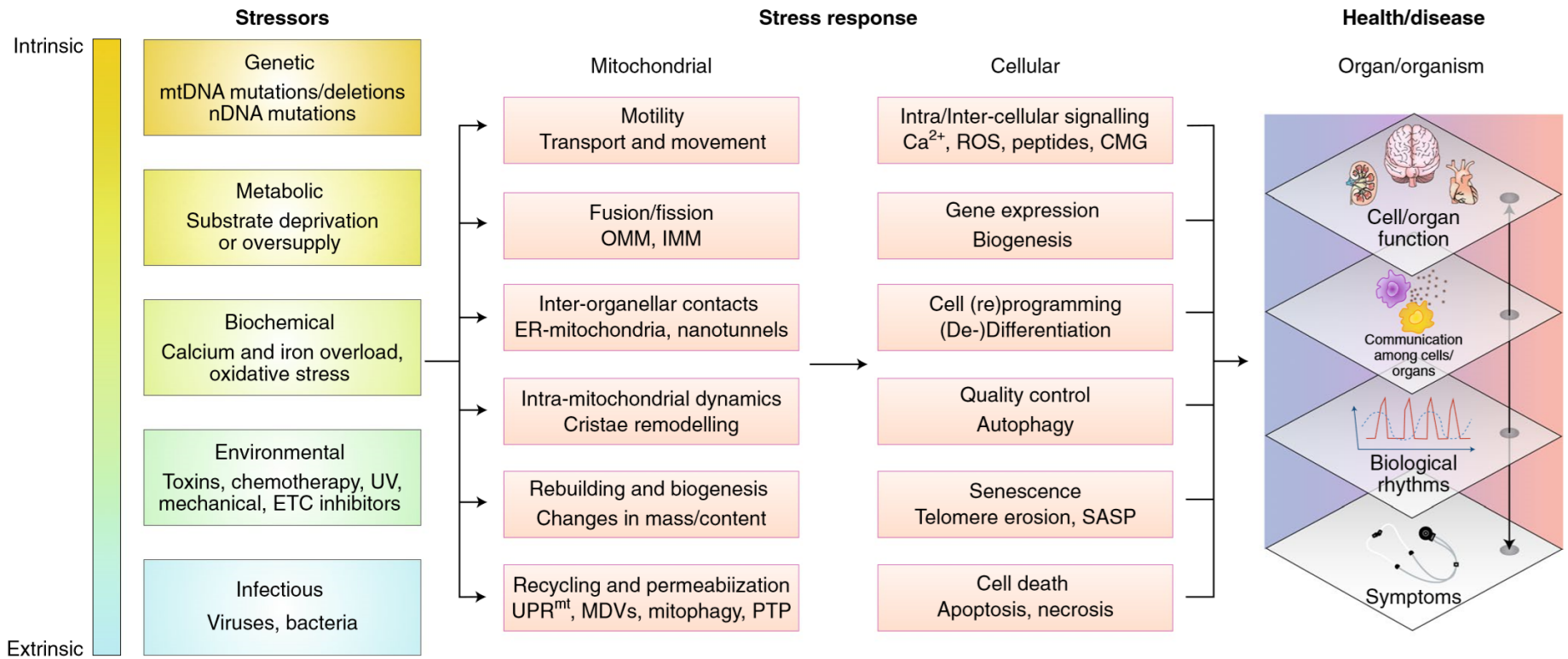
nature cell biology

FOCUS | REVIEW ARTICLE

https://doi.org/10.1038/s41556-018-0133-0

Mitochondrial dynamics in adaptive and maladaptive cellular stress responses

Verónica Eisner[1], Martin Picard[2] and György Hajnóczky[3*]



ER STRESS
APOPTOSIS AUTOPHAGY
UPR unfolded protein response

REVIEWS

ER stress and the unfolded protein response in neurodegeneration

Claudio Hetz[1–3] and Smita Saxena[4]

Nature review Neurology august 2017

Aggregates and inclusions are associated with ER stress reaction

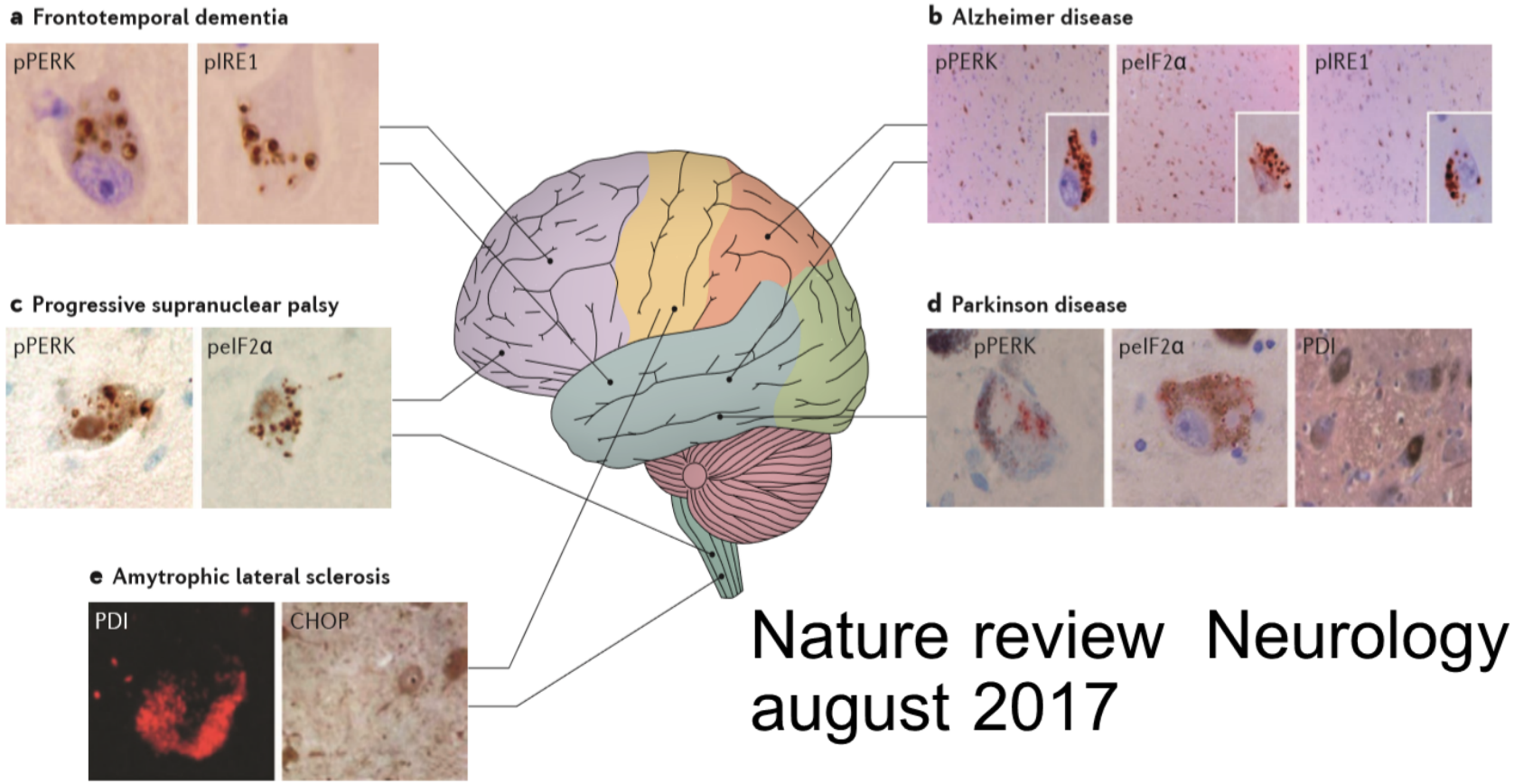


Figure 1 | **Protein aggregates in tissue from patients with neurodegenerative disease.** Most neurodegenerative diseases have distinct clinical manifestations, but they share accumulation of protein aggregates and inclusions that contain specific proteins in distinct brain regions; these aggregates are associated with an endoplasmic reticulum stress reaction. PDI, protein disulfide isomerase; p, phosphorylated; PERK, protein kinase RNA-like ER kinase; IRE1, inositol-requiring protein 1. Part **a** reproduced with permission from John Wiley and Sons © Nijholt, D. A. *et al. J. Pathol.* **226**, 693–702 (2012). Part **b** reproduced with permission from Elsevier © Jeroen, J. M. *et al. Am. J. Pathol.* **174**, 1241–1251 (2009). Part **c** reproduced with permission from BioMed Central © Stutzbach, L. D. *et al. Acta Neuropathol. Commun.* **1**, 31 (2013). Part **d** reproduced with permission from Elsevier © Hoozemans, J. J. *et al. Biochem. Biophys. Res. Commun.* **354**, 707–711 (2007) (left and middle panels) and © Conn, K. J. *et al. Brain Res.* **1022**, 164–172 (2004) (right panel). Part **e** reproduced with permission from Elsevier © Atkin, J. D. *et al. Neurobiol. Dis.* **30**, 400–407 (2008) (left panel) and © Ito, Y. *et al. Neurobiol. Dis.* **36**, 470–476 (2009) (right panel).

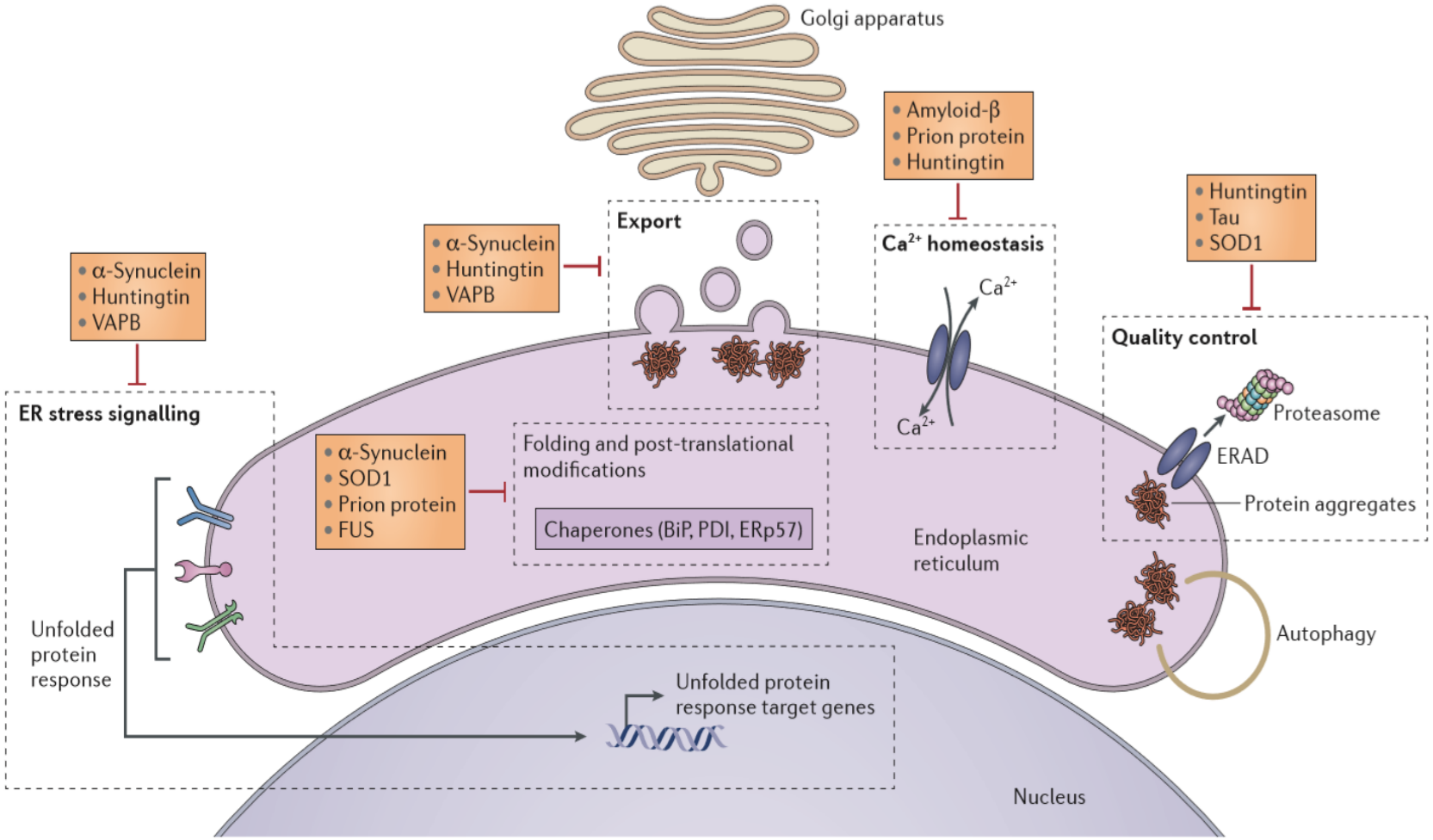


Figure 4 | **Mechanisms that trigger ER stress in neurodegenerative disease.** Correctly folded proteins are processed in the endoplasmic reticulum (ER) and trafficked to the Golgi apparatus for further maturation and distribution to their final destination. Protein folding and maturation at the ER is altered in neurodegenerative disease owing to the effects of protein aggregates on various mechanisms, which include inhibition of protein folding by inhibiting chaperones, interference with the ER-associated degradation pathway, perturbation of ER-to-Golgi trafficking, inhibition of proximal unfolded protein response components, and exacerbation of ER calcium release. ERAD, ER-associated degradation; FUS, fused in sarcoma; PDI, protein disulfide isomerase; SOD1, superoxide dismutase 1; VAPB, vesicle-associated membrane protein-associated protein B.

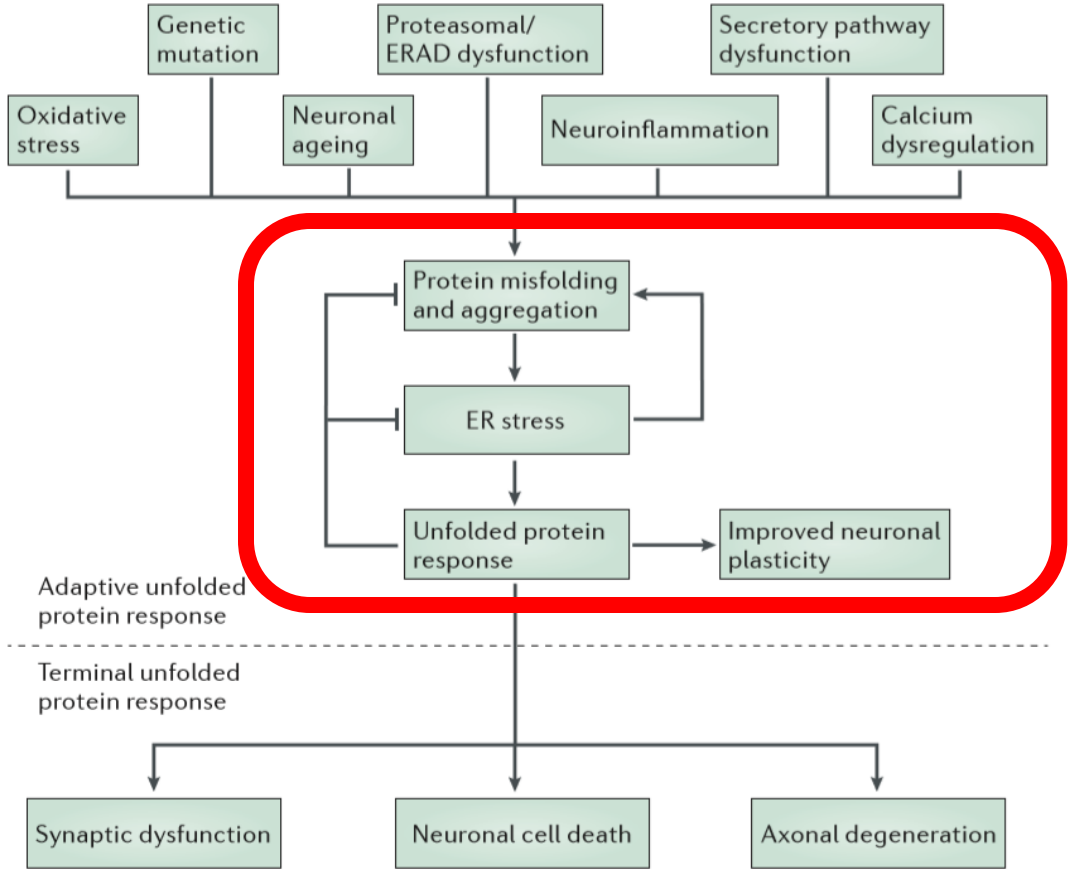


Figure 2 | **ER stress and proteostasis in neurodegenerative diseases.** Ageing, environmental factors and mutation of specific disease-related genes can trigger misfolding of a particular protein, leading to formation of aggregates that range from small oligomeric species to large inclusion bodies. This abnormal aggregation results in endoplasmic reticulum (ER) stress. ER stress can increase aggregation of disease-related proteins via a feedback loop by altering the folding and quality-control capacity of the cell or by altering the expression of disease-related genes. ER stress engages unfolded protein response (UPR) sensors that activate distinct downstream responses to improve protein folding and quality-control mechanisms to reduce ER stress. Long-term ER stress over-rides the adaptive responses of the UPR, and induces apoptosis. Chronic inhibition of protein synthesis can also reduce synthesis of synaptic proteins, thereby impairing neuronal function. ERAD, ER-associated degradation.

AD & dementia 2016 (Calsoralo,Edison)

M1 inflammatory
M2 anti-inflammatory

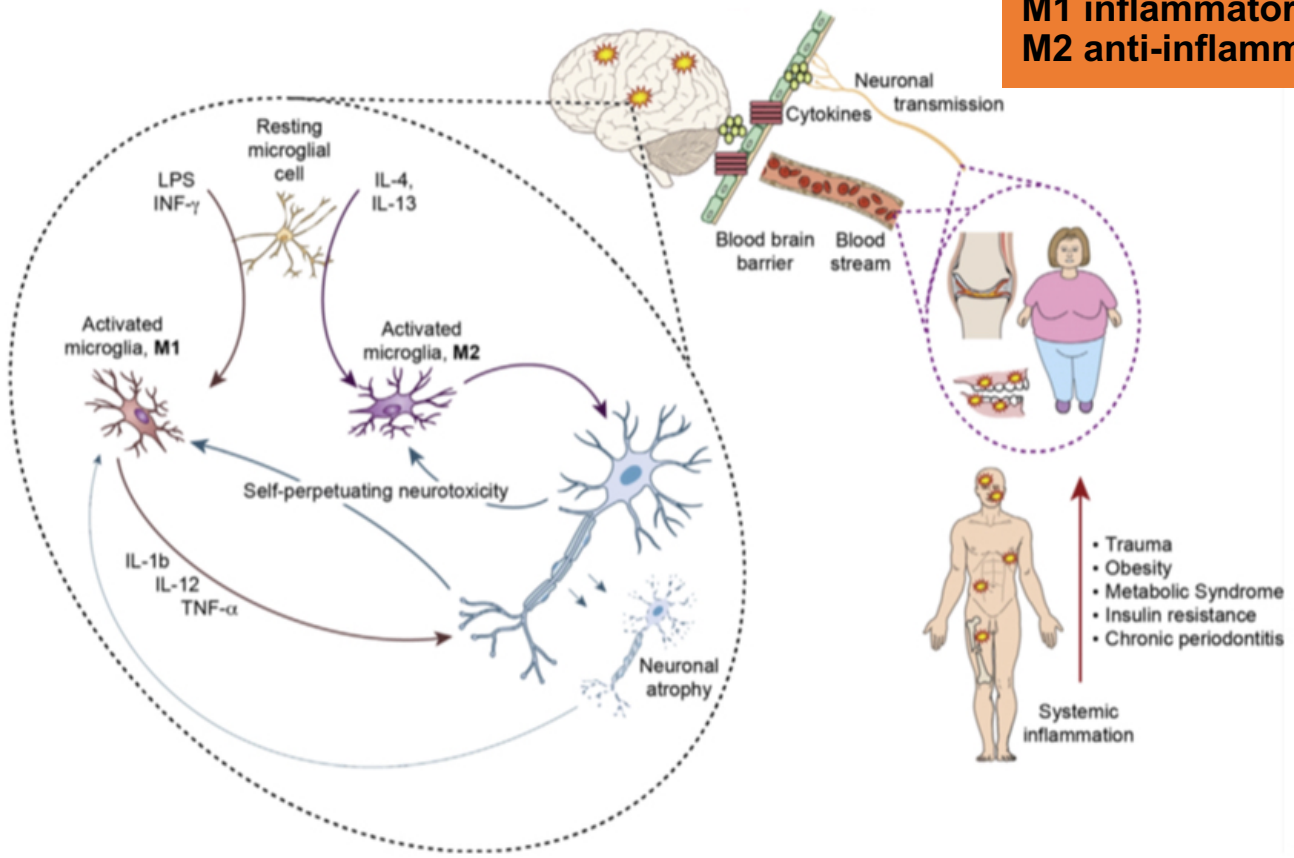


Fig. 1. Different mechanisms involved in microglial activation and neuronal damage in Alzheimer's disease. The activation pattern of microglial cells allows these cells to exist in two different phenotypes. M1, or classically activated, responds to LPS in combination with IFN-γ, that produces a massive inflammatory response releasing IL-1β, IL-12, TNF-α, and iNOS. M2, or alternatively activated, responds to IL-4 and IL-13, with an anti-inflammatory profile. It is known that obesity can promote neurodegeneration, being a low-grade inflammatory status, characterized by pro-inflammatory cytokine release and insulin/IGF-1 resistance. It has been demonstrated that increased plasma antibodies against periodontal bacteria and TNF-α in AD are independently associated with AD. It is also known that, in elderly patients, hip fracture may be responsible for delirium development, because the fracture itself and subsequent surgery are two events that can lead to a systemic inflammatory response.

รถเก็บขยะ

ไม่ตายเอง

Trends in Molecular Medicine

CellPress

Focus Issue: Feature Review

TREM2, Microglia, and Neurodegenerative Diseases

Felix L. Yeh,[1,*] David V. Hansen,[2] and Morgan Sheng[2,*]

Model of the Role of TREM2 in Alzheimer's Disease

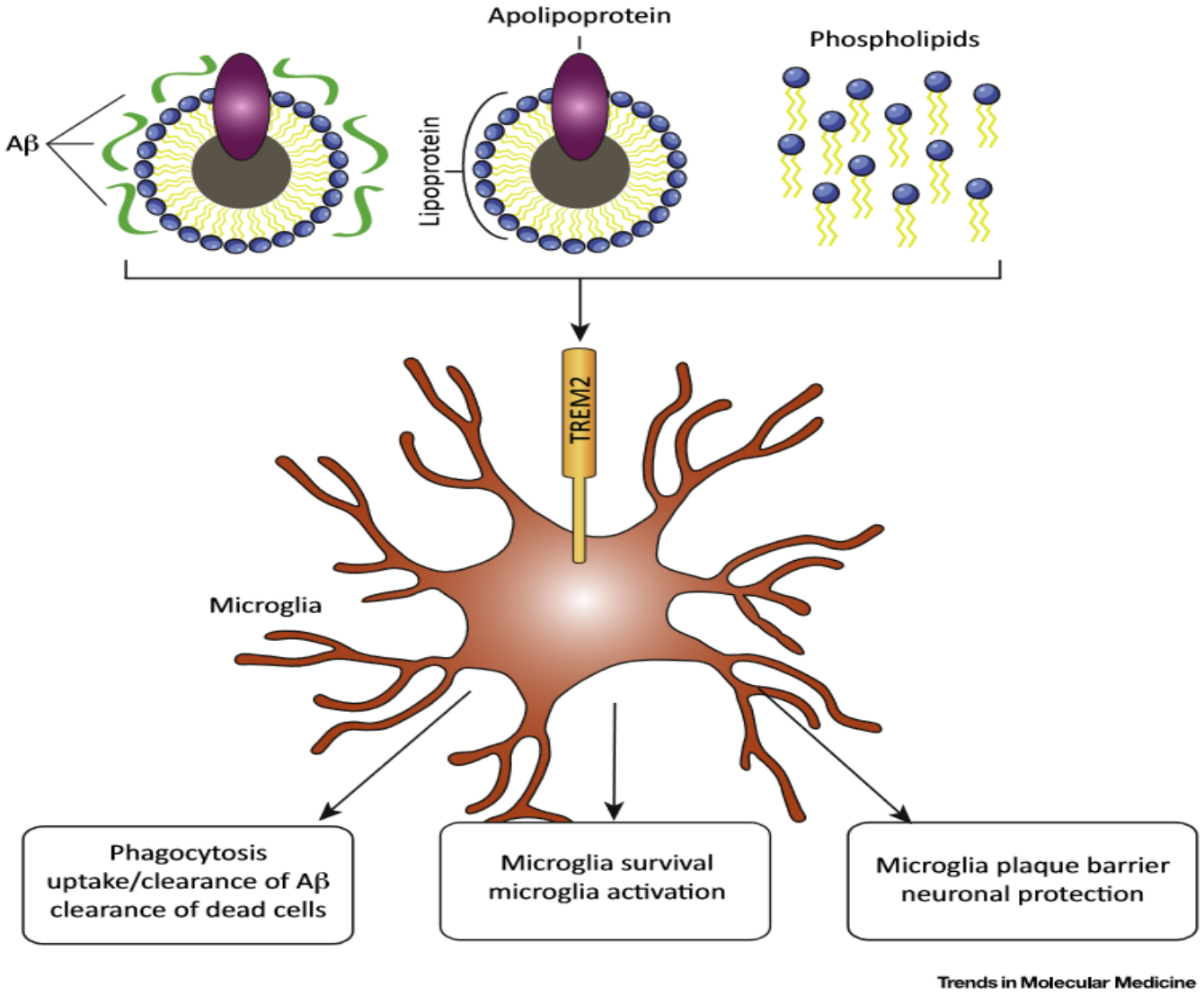


Figure 6. Phospholipids, apolipoproteins, and lipoproteins bind to TREM2, promoting microglia activation, survival, and the formation of a microglia barrier around amyloid plaques. In addition, association of Aβ with lipoproteins containing APOE or CLU may help to deliver these complexes to microglia, leading to increased amyloid clearance. TREM2 activity also prevents neuritic dystrophy. sTREM2 may compete for TREM2 ligands, preventing their interaction with membrane-bound TREM2 on microglia.

รถเก็บขยะ
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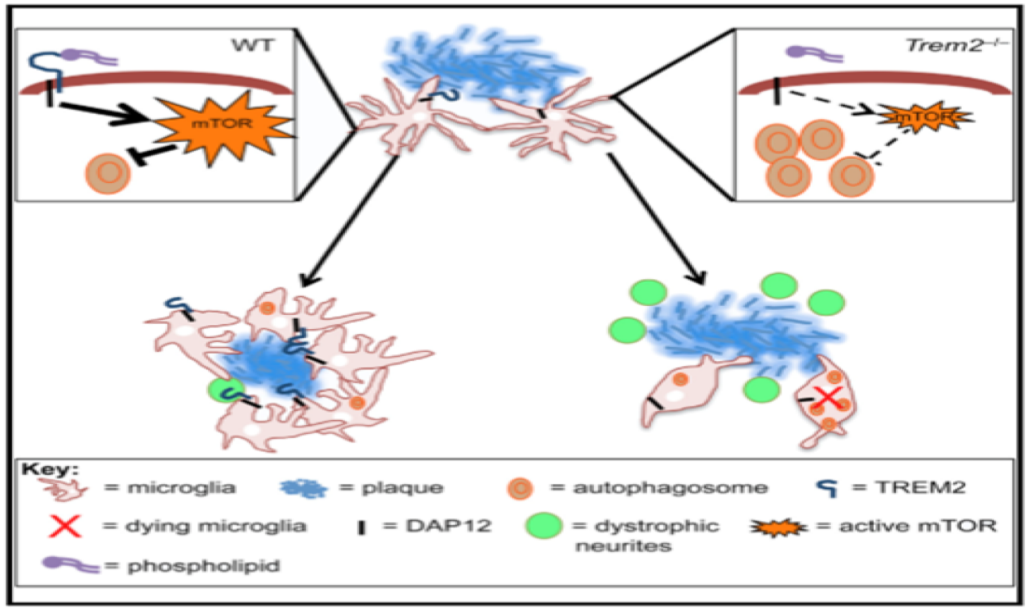
Cell

TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease

Graphical Abstract



Highlights

- TREM2-deficient microglia undergo increased autophagy in an AD mouse model
- Microglia in humans with AD-risk-associated *TREM2* alleles display marked autophagy
- TREM2 deficiency impairs microglial mTOR activation and metabolism
- Cyclocreatine improves microglia metabolism and pathology in TREM2-deficient AD mice

Authors

Tyler K. Ulland, Wilbur M. Song, Stanley Ching-Cheng Huang, ..., Maxim N. Artyomov, David M. Holtzman, Marco Colonna

Correspondence

mcolonna@wustl.edu

In Brief

The Alzheimer's disease risk factor TREM2 regulates microglial function through modulation of cellular biosynthetic metabolism.

We found that the defective mTOR signaling in TREM2-deficient microglia is associated with a compensatory increase of autophagy in vitro and in vivo in AD. Reduced glycolysis and autophagy are known to attenuate inflammation (Netea-Maier et al., 2016) and, indeed, microglia from 5XFAD mice lacking TREM2 weakly express inflammatory mediators in comparison to microglia from 5XFAD mice (Wang et al., 2015). Moreover, autophagy may also enhance microglial clearance of Aβ (Cho et al., 2014; Lucin et al., 2013; Shibuya et al., 2014), as it does in neurons (Hara et al., 2006; Komatsu et al., 2006; Yang et al., 2011). However, a long-term defect in mTOR activation results in global microglial dysfunction, reduced cell viability, and proliferation, as demonstrated by increased caspase-3 activation in microglia and by the previously reported increase in dying microglia around plaques in *Trem2*$^{-/-}$ 5XFAD mice (Wang et al., 2015). Thus, while increased autophagy may be beneficial in reducing inflammation and Aβ load in the short-term, a defect in mTOR signaling is detrimental and severely impairs microglia fitness and capacity to respond to Aβ accumulation in the long-term.

Ulland et al., 2017, Cell *170*, 649–663
August 10, 2017 © 2017 Elsevier Inc.
http://dx.doi.org/10.1016/j.cell.2017.07.023

CellPress

Trends in Molecular Medicine 2017

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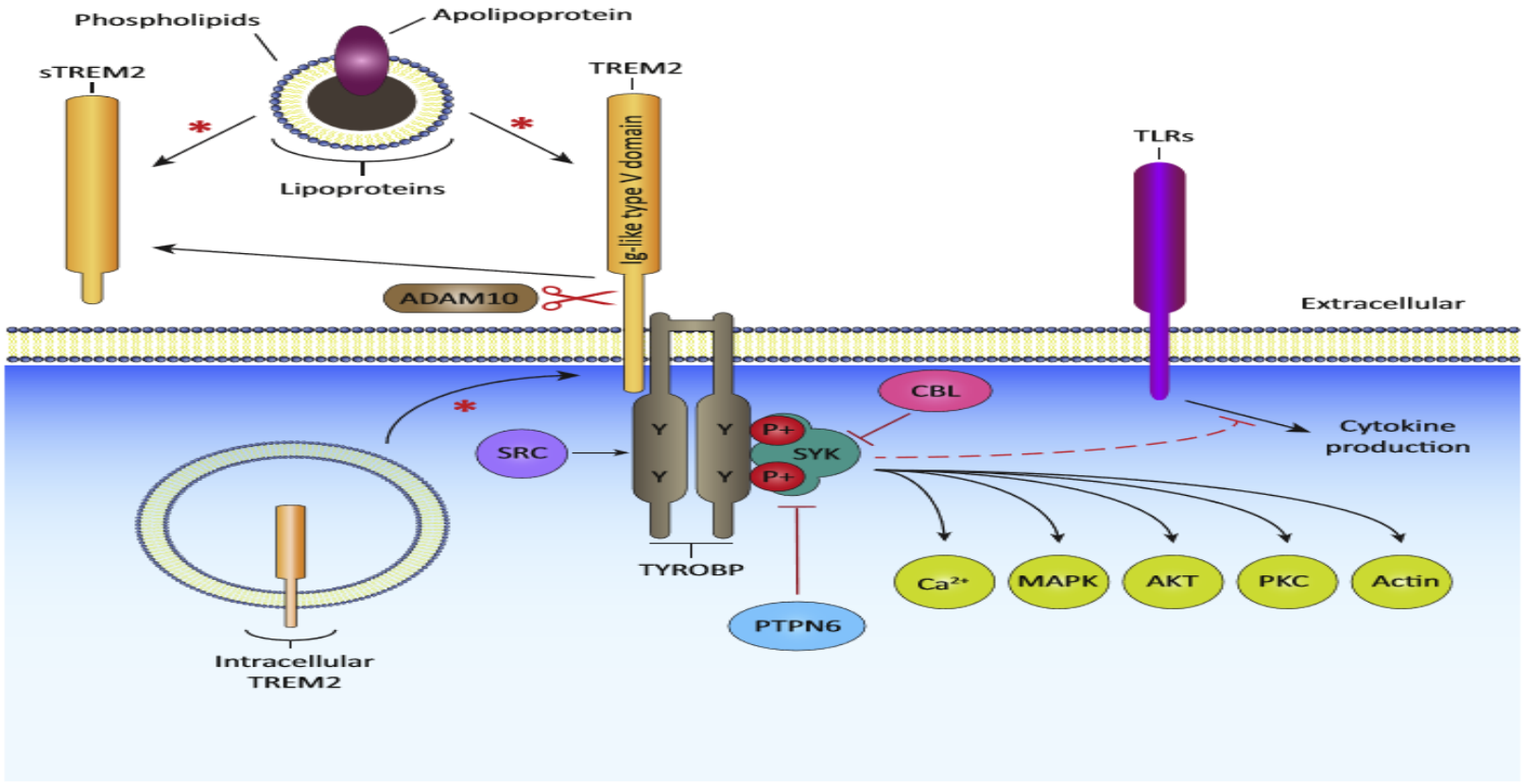

Trends in Molecular Medicine

Figure 1. Regulation of TREM2 Signaling. TREM2 binds to phospholipids, apolipoproteins, and lipoproteins through its immunoglobulin (Ig)-like V-type domain. Surface levels of TREM2 can be regulated by shedding (cleavage by ADAM10 to produce soluble sTREM2) or through trafficking from intracellular stores of TREM2. Upon ligand binding, SRC family tyrosine-protein kinases phosphorylate the tyrosine residues within the ITAM domain of TYROBP (a disulfide-linked homodimer). Spleen tyrosine kinase (SYK) is then recruited, initiating a host of downstream signaling events such as Ca^{2+}, MAPK, RAC serine/threonine-protein kinase (AKT), protein kinase C (PKC), and actin mobilization. SYK signaling can be negatively regulated through PTPN6, which dephosphorylates the ITAM domain of TYROBP, and also by CBL, an E3-ubiquitin ligase. TREM2–TYROBP signaling attenuates the production of proinflammatory cytokines in response to activation of Toll-like receptors (TLRs). Asterisks denote processes affected by disease-associated TREM2 variants.

Amyloid-microglia as defensive line against virus!!!!!

- **NIH-led public-private partnership, Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD) (started 2013)**
- **876 brains—healthy and early- or late-stage Alzheimer's.**
- **DNA and RNA sequencing to parse out genetic differences between the groups as well as differences in how inherited genes were expressed or made into RNA.**

Amyloid-microglia as defensive line against virus!!!!!

- **pattern for viral biology**
- **more viral DNA in Alzheimer's brains compared with healthy brains— high levels of DNA from human HHV-6A**
- **RNA of both HHV-6A and HHV-7 were also higher in the Alzheimer's brains than in healthy brains, and viral RNA levels tracked with the severity of clinical symptoms**

HHV-6A is a usually symptom-less virus that infects people later in life. HHV-7 infects more than 80 percent of infants, often causing a rash.

Amyloid-microglia as defensive line against virus!!!!!

- **a biological social network to probe how various molecular and genetic signals were interacting with each other**
- **viral genes were influencing other known Alzheimer's genes and molecules—evidence that the viruses are directing at least part of the disease process.**

The viruses "seemed to be talking to some of the networks that contained some of the familiar Alzheimer's-related genes."

- **A microRNA** is suppressed by the HHV-6A virus in Alzheimer's brains
- mice deficient in this microRNA, developed larger and more abundant amyloid plaques in their brains than did mice with normal microRNA levels.
- Sam Gandy, a co-author Mount Sinai neurologist and amyloid expert/Dudley HSV-1
- Moir: amyloid as innate immunity
- **Neuron June 21st 2018**

Role of HSV-1 and Rx effect (Taiwan study)

- Treated individuals infected with HSV-1 (cold sores) were 90 percent less likely to develop senile dementia than those who weren't treated

amyloid beta peptides bind to and entrap HSV-1 and HHV-6 infection hypothesis

- Mice infected with these herpes viruses quickly accumulate beta amyloid plaques
- beta amyloid plaques build up during an infection, trigger inflammation and other unhelpful responses, such as the creation of tau tangles that kill neurons.
- The plaques alert microglia an immune cascade that kills even more neurons.

Progress in Neurobiology 160 (2018) 82–100

Contents lists available at ScienceDirect

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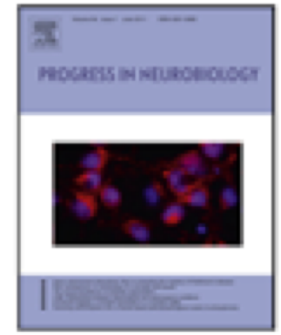

Review article

The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: Clues for other neuroinflammatory diseases

Valerio Chiurchiù[a,b], Mario van der Stelt[c], Diego Centonze[d,e,1], Mauro Maccarrone[a,b,*,1]

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[e] IRCCS Istituto Neurologico Mediterraneo Neuromed, Via Atinense 18, 86077 Pozzilli, IS, Italy

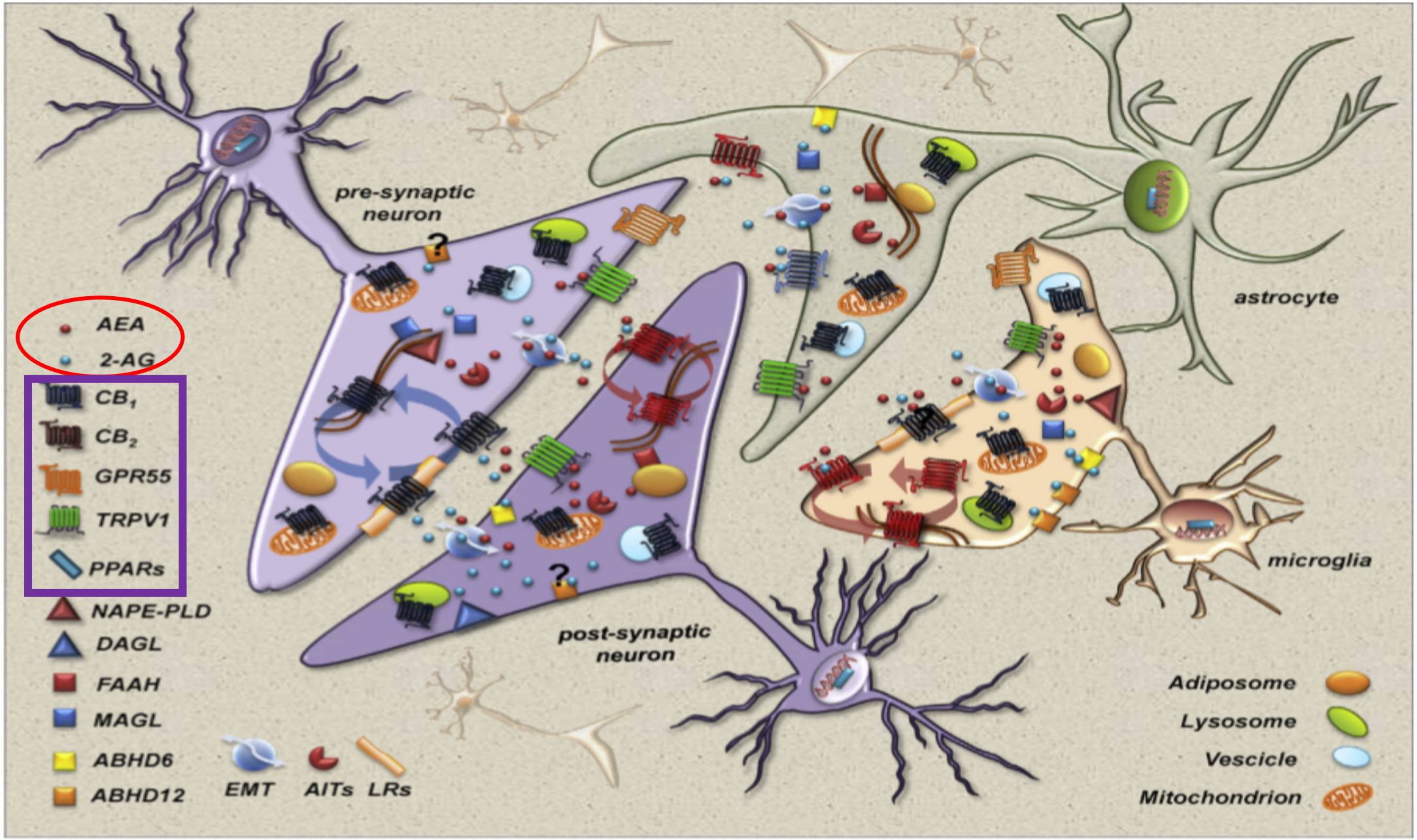

pre-synaptic neuron
post-synaptic neuron
astrocyte
microglia
AEA
2-AG
CB1
CB2
GPR55
TRPV1
PPARs
NAPE-PLD
DAGL
FAAH
MAGL
ABHD6
ABHD12
EMT
AITs
LRs
Adiposome
Lysosome
Vescicle
Mitochondrion

Fig. 3. A modern view of the eCB system in the CNS. eCB signaling is orchestrated by target receptors (CB_1, CB_2, GPR55, TRPV1 and PPARs), biosynthetic (NAPE-PLD and DAGL) and degradative (FAAH, MAGL, ABHD6 and ABHD12) enzymes, transmembrane transport mechanisms (like the putative EMT), intracellular trafficking by AITs like fatty acid binding proteins, heat shock protein 70, and FAAH-like AEA transporter, as well as by storage organelles (adiposomes or lipid droplets). Altogether, these proteins regulate the endogenous tone of eCBs, and hence their biological activity. For some of the elements of the eCB system a distinct distribution, both intracellularly and among pre- and post-synaptic neurons, microglia and astrocytes, has been documented. It should be noted that, unlike other eCB-binding receptors, CB_1 appears to be located in cholesterol-enriched membrane microdomains termed LRs, and that CB_2 is expressed in neurons mainly upon brain injury. Moreover, the role in neuroinflammatory diseases of eCB system elements shown here but not listed in Table 1 remains to be elucidated.

Abbreviations: ABHD6/12, α-β-hydrolase domain 6/12; AITs, AEA intracellular transporters; CB_1/CB_2, G-protein coupled type-1 and type-2 cannabinoid receptors; DAGL, diacylglycerol lipase α/β; eCBs, endocannabinoids; EMT, putative endocannabinoid transmembrane transporter; FAAH, fatty acid amide hydrolase; GPR55, G-protein coupled receptor 55; LRs, lipid rafts; MAGL, monoacylglycerol lipase; NAPE-PLD, N-acylphosphatidylethanolamine-specific phospholipase D; PPARs, peroxisome proliferator-activated nuclear receptors; TRPV1, transient receptor potential vanilloid 1 channels.

ระบบ **e cannabinoid**
ต่อต้านการอักเสบที่เกิดจาก
สาร **IL 1beta TNF**
ซึ่งจะเหนี่ยวนำ สารสื่อประสาทในทาง
เลว และต้านตัวดี

พระเอกเป็นผู้ร้าย
ผู้ร้ายเข้าพวกกับพระเอก

**Receptor at
where and of
which system?**

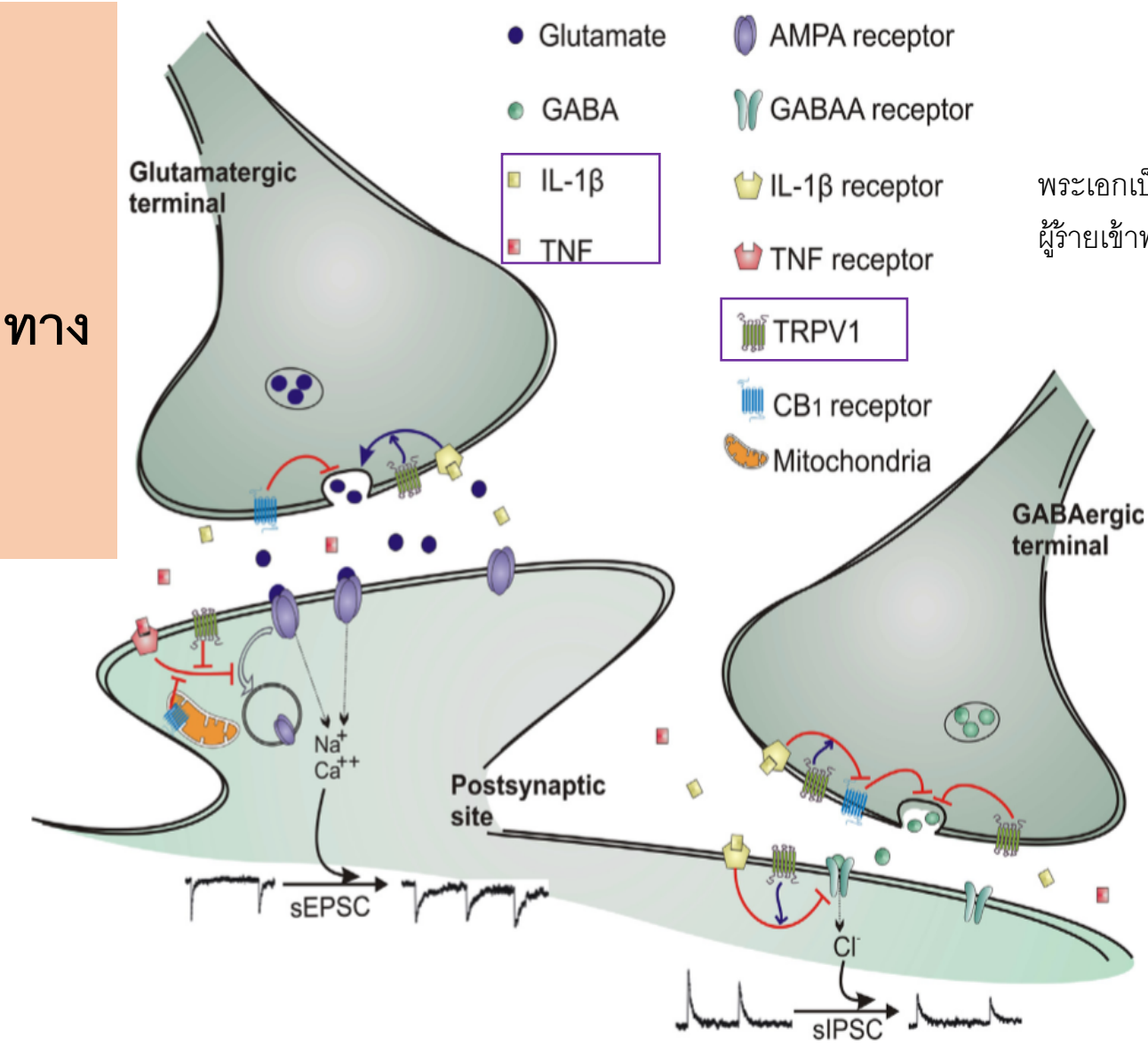


Fig. 4. Overall scheme of the presynaptic and postsynaptic perturbations mediated by proinflammatory cytokines and modulated by eCB system in EAE. IL-1β increases glutamate release at presynaptic terminals and TNF induces AMPA receptor upregulation, resulting in enhanced glutamate transmission. CB_1 contrasts the effects of IL-1β by reducing the frequency of spontaneous glutamate-mediated synaptic currents on presynaptic terminals, conversely TRPV1 is permissive for IL-1β synaptic effects on glutamate transmission. At the postsynaptic site, both CB_1 and TRPV1 restrain TNF-mediated potentiation on postsynaptic AMPA receptor. Moreover, IL-1β promotes the inhibition of CB_1 function on GABAergic synapses, thus mitigating the reduction of GABA release. Moreover, IL-1β reduces postsynaptic GABAA receptor function by promoting the decrease of GABA signaling. Finally, TRPV1 channels are permissive for IL-1β synaptic effects at both pre- and postsynaptic sites.

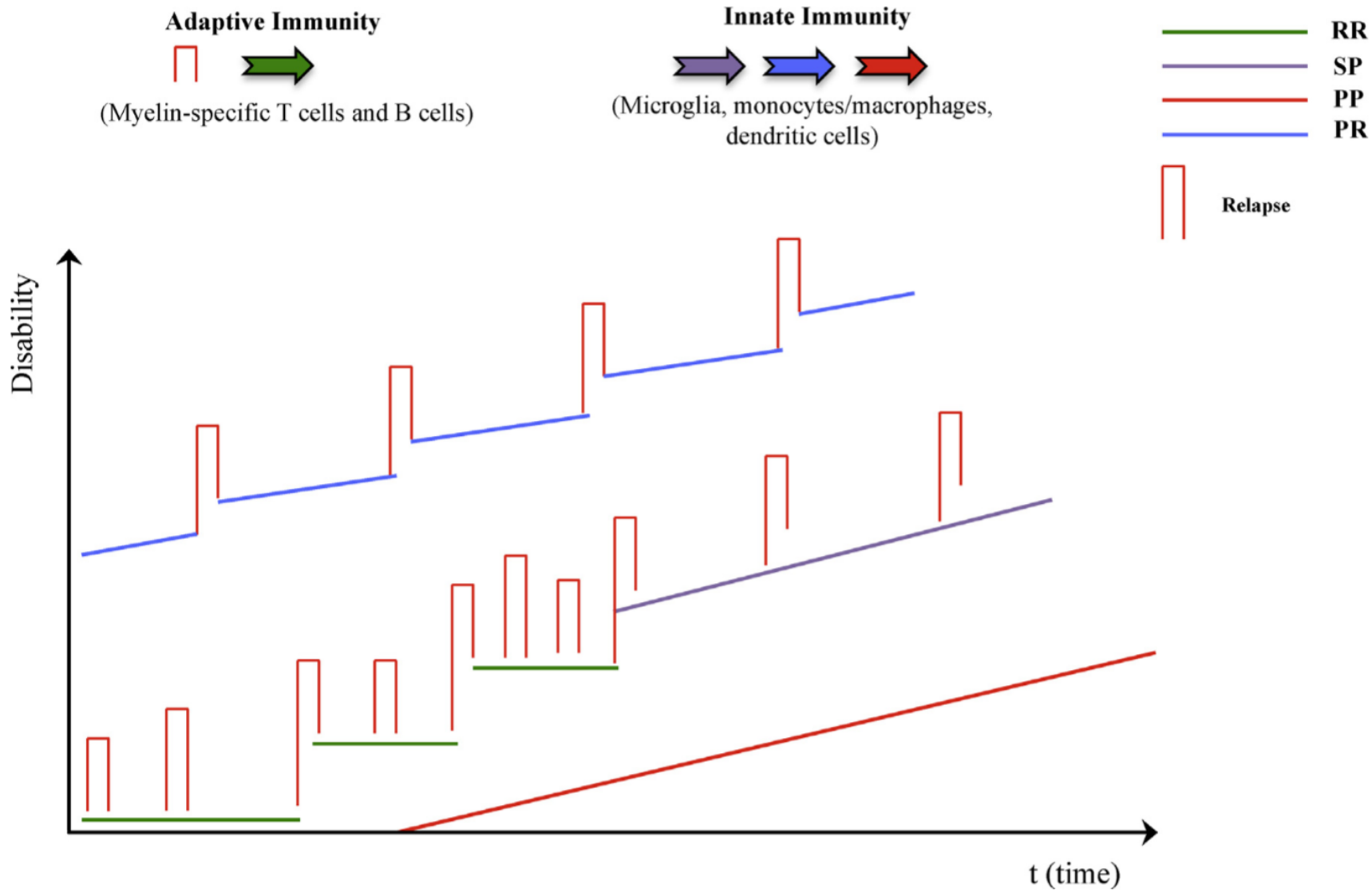


Fig. 1. The immunological basis of the different clinical forms of MS.

ลักษณะการดำเนินโรคสะท้อนถึงกลไกของระบบภูมิคุ้มกันที่ผิดปกติ เกิดการอักเสบจากกระบวนการแบบต้นและปลาย และมีผลกระทบต่อโครงสร้างของสมองในที่เปลือกหรือแกนประสาท รวมทั้งเหนี่ยวนำให้เซลล์ในสมองทำตัวเป็นศัตรู

Table 2
Alterations of distinct elements of the eCB system, and their role in inflammation and neurodegeneration in MS.

ECS element	Model	Sample	Variation	Effects	Reference
AEA	Chronic EAE	Brain, spinal cord	↑	Early inhibition of spasticity	Baker et al. (2001)
	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	RR-MS	Autopsied brain	↑	Microglia-induced neuroprotection	Eljaschewitsch et al. (2006)
	EAE and RR-MS patients	Brain, CSF, plasma, T cells	↑	Neuroprotection	Centonze et al. (2007a)
	RR-MS, SP-MS	CSF	↓	–	Di Filippo et al. (2008)
	RR-MS, PP-MP, SP-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	RR-MS	T cells, B cells, NK cells	↑	–	Sánchez López et al. (2015)
NAPE-PLD/ FAAH	EAE and RR-MS patients	Brain, CSF, plasma, T cells	↑ NAPE-PLD and ↓FAAH	Neuroprotection	Centonze et al. (2007a)
	SP-MS	Plasma	↓FAAH	Disease progression	Jean-Gilles et al. (2009)
	RR-MS	mDC and pDC	↓FAAH in mDC and ↑ in pDC	Lack of immunoregulation	Chiurchiù et al. (2013)
	RR-MS	T cells, B cells, NK cells	←→	–	Sánchez López et al. (2015)
2-AG	Chronic EAE	Brain, spinal cord	↑	Late inhibition of spasticity	Baker et al. (2001)
	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	RR-MS patients	CSF	←→	–	Centonze et al. (2007a)
	RR-MS, SP-MS	CSF	↓	–	Di Filippo et al. (2008)
	TMEV-IDD	Spinal cord	↑	–	Loría et al. (2008)
	RR-MS	T cells, B cells, NK cells	Increased in NK cells	–	Sánchez López et al. (2015)
DAGL/ MAGL	EAE	–	–	Inhibition of MAGL ameliorates EAE progression	Hernández-Torres et al. (2014)
CB_1	Lewis EAE rats	Brain	↓	Worsening of disease development and neurological impairment	Cabranes et al. (2005)
	P-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	MS plaques	Neurons, oligodendrocytes, infiltrated T cells	↑	Disease progression	Benito et al. (2007)
	RR-MS	T cells, B cells, NK cells	↑in T cells	–	Sánchez López et al. (2015)
CB_2	TMEV-IDD	Spinal cord	↑	–	Loría et al. (2008)
	P-MS	Plasma	↑	Disease progression	Jean-Gilles et al. (2009)
	MS plaques	Infiltrated T cells, astrocytes, microglia	↑	Disease progression	Benito et al. (2007)
	RR-MS	mDC and pDC	↑in mDC and ←→in pDC	Lack of immunoregulation	Chiurchiù et al. (2013)
	RR-MS	T cells, B cells, NK cells	Increased in B cells	–	Sánchez López et al. (2015)

CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; mDC, myeloid dendritic cells; RR, relapsing-remitting; P, progressive; pDC, plasmacytoid dendritic cells; PP, primary progressive; SP, secondary progressive; TMEV-IDD, Theiler's murine encephalomyelitis virus-induced demyelinating disease. ↑, increase; ↓, decrease; ←→, unchanged.

สัตว์ทดลอง

คน

แบบและระยะต่างๆของโรค

กลไลที่เกิดขึ้นใน

ระยะต่างๆ

เซลล์ในสมอง

เซลล์ในระบบภูมิคุ้มกัน

ระบบ

eCannabinoid

จาก MULTIPLE SCLEROSIS-ALZHEIMER/PARKINSON'S DISEASES (NEUROINFLAMMATORY-MISFOLDED PROTEIN-NEURODEGENERATIVE)

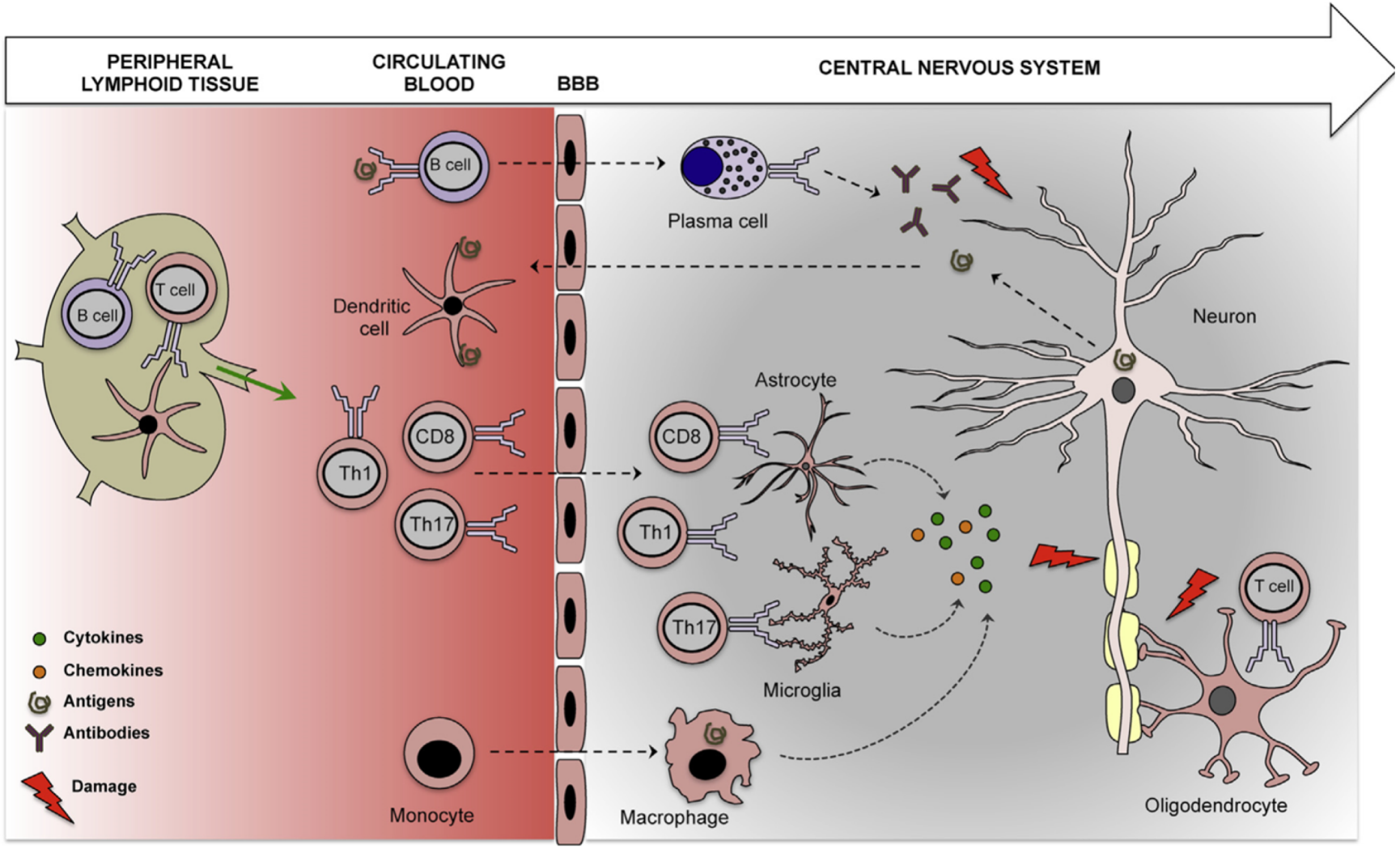


Table 4
Alterations of distinct elements of the eCB system in neuroinflammatory diseases other than MS (pertinent references are in parenthesis).

ECS element	AD	PD	HD	ALS
AEA	↓AEA in brain (Jung et al., 2012)	↑AEA in basal ganglia, CSF and blood (Pisani et al., 2011; Di Filippo et al., 2008)	↓AEA in basal ganglia (Lastres-Becker et al., 2003) ↑AEA in blood (Battista et al., 2007)	↑AEA in spinal cord (Witting et al., 2004)
NAPE-PLD/ FAAH	↑FAAH in astrocytes and microglia (Benito et al., 2003)	–	↓NAPE-PLD and FAAH in striatum (Bari et al., 2013) ↓FAAH in blood (Battista et al., 2007)	–
2-AG	↑in brain (van der Stelt et al., 2006; Altamura et al., 2015)	↑in basal ganglia (Pisani et al., 2011)	↓in basal ganglia (Lastres-Becker et al., 2003)	↑in spinal cord (Witting et al., 2004)
DAGL/MAGL	↑DAGL in brain (van der Stelt et al., 2006; Altamura et al., 2015)	–	↓DAGL in striatum (Bari et al.[115]) ↓MAGL in cortex (Bari et al., 2013)	–
CB_1	↓in hippocampus and frontal cortex (Westlake et al., 1994; Ramirez et al., 2005) ←→in astrocytes and microglia (Benito et al., 2004)	↑in basal ganglia (Pisani et al., 2011)	↓in neuropeptide Y interneurons (Horne et al., 2013) ↓in GABAergic neurons (Centonze et al.[120])	↑in spinal cord and motor neurons (Witting et al., 2004; Zhao et al., 2008)
CB_2	↑in astrocytes and microglia (Benito et al., 2003)	–	–	in spinal cord and microglia (Witting et al., 2004; Yiangou et al., 2006)

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; HD, Huntington's disease; PD, Parkinson's disease. ↑, increase; ↓, decrease; ←→, unchanged.

ยีน

ศพ
สัตว์
ทดลอง

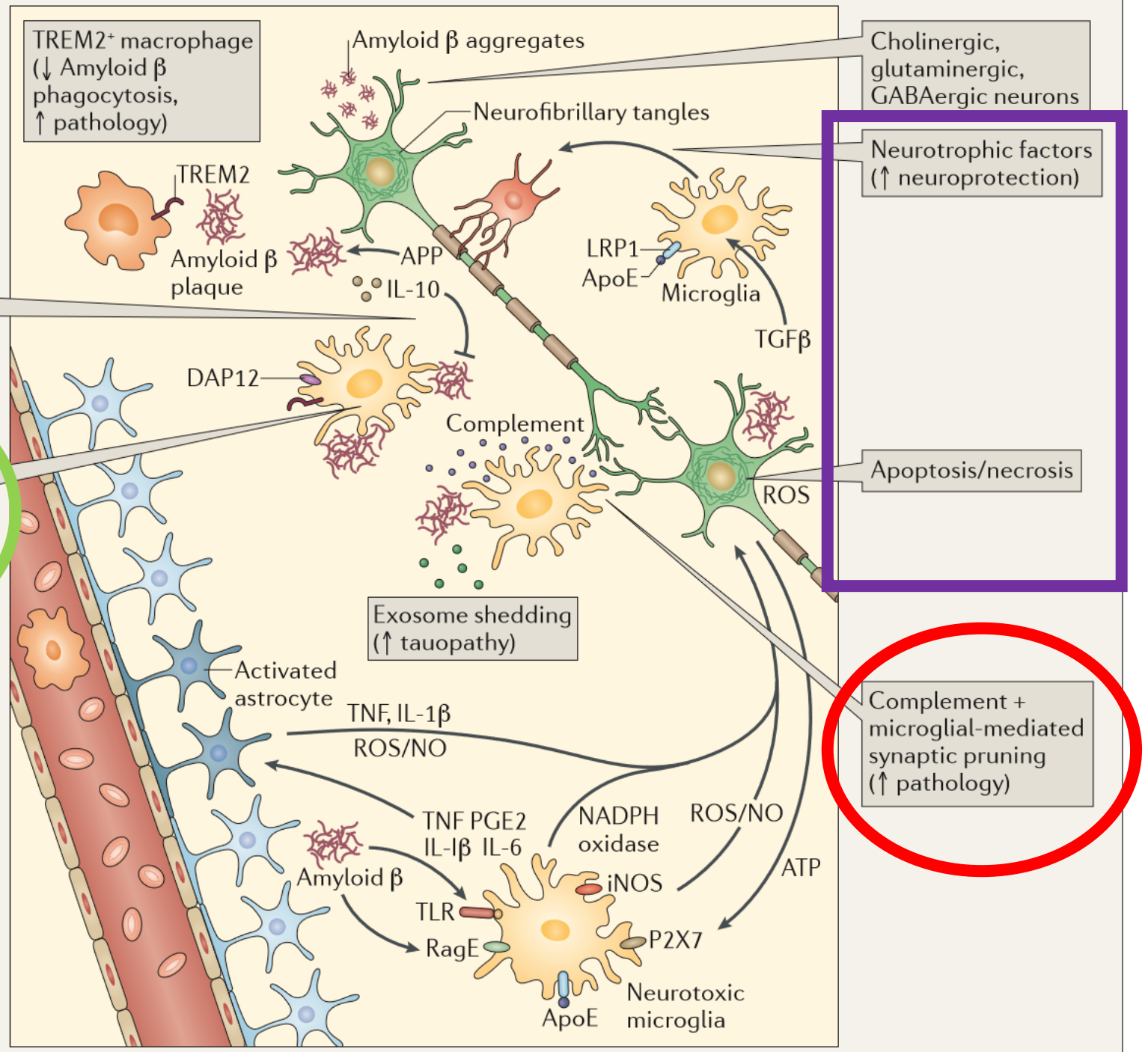
คน

Alzheimer disease (AD)

Genomics
- Implicates innate (myeloid and glial) immune genes in predisposition to AD

Phenomics
- Postmortem brain tissue analyses demonstrate prominent neuroinflammatory signatures, implicating activated glial cells
- In-depth mechanistic studies in disease models suggest diversity of neuroinflammatory mechanisms

Clinical and paraclinical data
- Investigations to facilitate patient stratification and to identify predictors of neuropathology



NATURE REVIEWS | NEUROLOGY
VOLUME 12 | DECEMBER 2016

NEUROLOGICAL HEALTH

For Alzheimer's Sufferers, Brain Inflammation Ignites a Neuron-Killing "Forest Fire"

And it could also be the kindling sparking Parkinson's and other neurodegenerative maladies

By Karen Weintraub on March 4, 2019

The best way to avoid Alzheimer's is to prevent it from ever starting, which might require keeping brain inflammation to a minimum, particularly in later life. Preventative measures are already well known: eat healthy foods, sleep well, exercise regularly, minimize stress and avoid smoking and heavy drinking.

Table 3. Proposed Classification of Neurological Manifestations of Influenza

	Acute Onset—Cytokine Storm	Subacute Onset—Adaptive Immune Responses	Late Onset—Unknown Pathophysiology
	Febrile seizures	Guillain-Barré syndrome	Post–viral parkinsonism
	Acute movement disorder	Transverse myelitis	Encephalitis Lethargica
	Acute benign encephalopathy/encephalitis	Acute disseminated encephalomyelitis (ADEM)	
	Acute encephalopathy syndromes (AESs): Mild encephalitis/encephalopathy with reversible splenial lesion (MERS)	Myositis	
	Posterior reversible encephalopathy syndrome (PRES)	Cerebellitis	
	Acute necrotizing encephalopathy (ANE)		
	Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)		
	Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF)		
Increasing neurological sequelae and mortality	Acute shock with encephalopathy and multiorgan failure (ASEM)[a]		
	Acute hemorrhagic leukoencephalopathy (AHL)		

[a] Proposed revised nomenclature for hemorrhagic shock and encephalopathy syndrome (HSES).

Source: Adapted from Akins et al [8].

ACUTE ONSET

DIRECT EFFECT?

Some affect BBB

Some affect Neuronal function

Should we include autoimmune response:
Neuronal surface/synaptic
Intracellular antigen?

Neurological Manifestations of Influenza Infection in Children and Adults: Results of a National British Surveillance Study

Ana Gomika,[1] Benedict B. Michael,[1] Elizabeth Ledger,[1] Ian J. Hart,[2] Michael Ahmad,[3] Gabriel Chew,[3] James Lilleker,[4] Michael Lunn,[1] David McKee,[5] Deirdre Peaks,[5] Karen Pysden,[5,6] Mark Roberts,[5] Enitan D. Carrol,[1] Ming Lin,[1] Shivaram Avula,[1,7] Tom Solomon,[1] and Rachel Kneen[1]

ACUTE "VIRAL ENCEPHALITIS" SYNDROME

October 2010 and August 2012

- **Prospective study 103 Thai patients**
- **non-bacterial, non-rickettsial, non-TB, non-fungal and non-parasitic encephalitis and/or myelitis**
- **normal or lymphocytic CSF profile**
- **King Chulalongkorn Memorial Hospital (KCMH) and 17 hospitals**
- **Eleven pediatric patients aged 1-14 years**

Saraya *et al. BMC Neurology* 2013, **13**:150
http://www.biomedcentral.com/1471-2377/13/150

BMC Neurology

RESEARCH ARTICLE Open Access

Autoimmune causes of encephalitis syndrome in Thailand: prospective study of 103 patients

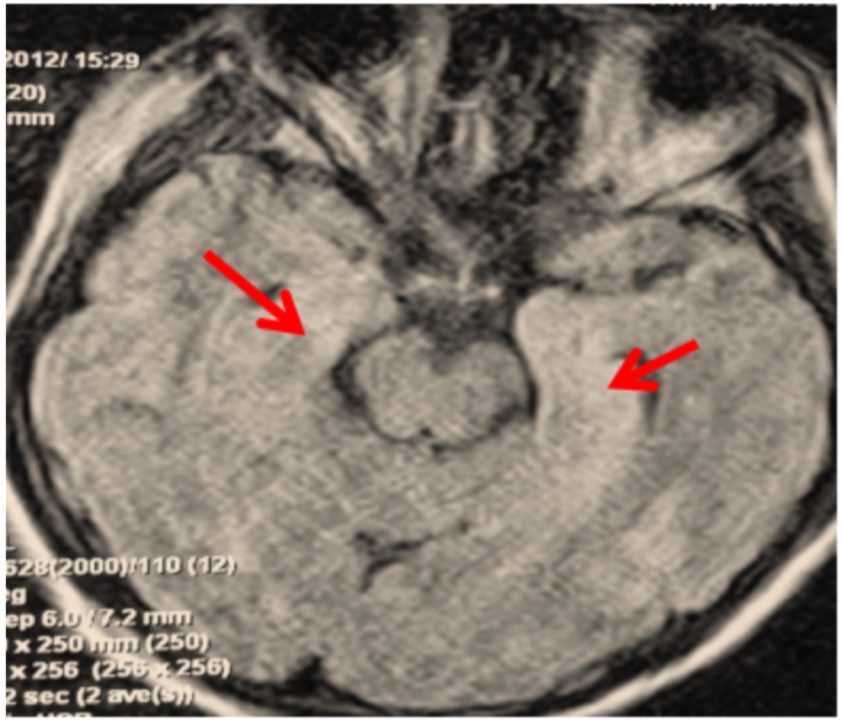
Abhinbhen Saraya[1,2*], Aekkapol Mahavihakanont[1,2], Shanop Shuangshoti[2,3], Nuntaporn Sittidetboripat[1,2], Tayard Deesudchit[4], Michael Callahan[5,6], Supaporn Wacharapluesadee[1,2], Henry Wilde[1,2] and Thiravat Hemachudha[1,2]

Clinical course & investigations	NMDA	Demyelinating diseases/NMO	AMPA	Behcet	ANNA2 (anti-Ri)	GABA	NMDA +ANNA2	VGKC	Anti-Yo	NPLE
Encephalitis: myelitis	4: 1	1: 2	0: 1	0: 1	5: 1	1: 0	1: 0	1: 0	2: 0	3: 1
Average age (yr)	39	52	2	33	67	70	18	67	16	31
	(5–43)	(8–56)			(25–82)				(11–21)	(23–50)
Female: male	4: 1	3: 0	1: 0	2: 0	3: 3	0: 1	0: 1	0: 1	1: 1	4: 0
Underlying disease	ovarian teratoma (1)	-	-	-	DM(1), SLE(1) Ovarian cancer (1)	alcoholic cirrhosis	hemophagocytic syndrome	DM	Germ cells tumor (1)	SLE (4)
Prodrome symptoms	headache (2), fever (1)	fever (1)	fever with rash	-	fever (2), URI (1), anorexia (1)	-	fever	fever + headache	fever (1), headache (1)	fever (2), weight loss (1), fatigue + rash + alopecia (1)
Presenting symptoms	psychosis + seizure (3), behavior change (1), quadripa resis (1)	behavior change ± Seizure (2), drowsy (1) parkinsonism (1)	stiff person	para paresis	psychosis ± seizure (2), Seizure (3), para paresis (1)	behavior change + Seizure (1)	seizure (1)	behavior change + Seizure (1)	behavior change (1), seizure (1)	behavior change (1), psychosis (1), seizure (1), paraparesis (1)
Average										
CSF wbc	32	5	0	157	1	0	0	0	30	0
(cells/mm^3)	(0–62)	(5–60)			(0–19)				(0–60)	(0–1)
Average CSF protein	30	45	22	55	40	36	58	51	43	99
(mg/dl)	(19–242)	(30–66)			(2–68)				(42–45)	(28–142)
Average CSF sugar (mg/dl)	62	73	59	40	83	71	53	149	70	65
	(44–102)	(27–104)			(50–95)				(67–73)	(47–82)
Imaging pattern	normal (1), meninges (1), multifocal (2)	white matter (1), brainstem + midline (1)	normal	myelo pathy	non-specific change (2), temporal lobe (2), multiple cortical lesions (1)	white matter (1)	cerebral atrophy(1)	meninges + cortex (1)	non-specific white matter change (1), miscellenous (1)	midline + cortex (1), non-specific white matter change (1)
Outcome	complete recovered (1), partially recovered (1), disable (3)	partially recovered (1), disable (2)	partially recovered,	disable	partially recovered (4), Disable (3)	dead	partially recovered	partially recovered	partially recovered (2)	partially recovered (1), disable (2), dead (1)

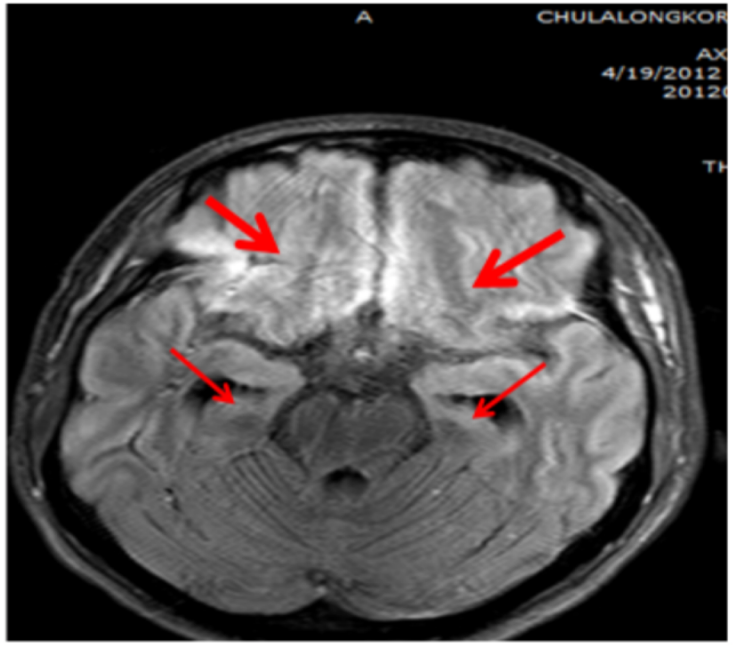
Anti-Yo paraneoplastic antibody
(purkinje cell cytoplasmic antibody - 1)

UNCONTROLLED SEIZURES

- Intravenous immunoglobulin (IVIG)
- After IVIG, seizures were gradually controlled with high doses antiepileptic drugs
- test for malignancy markers elevated CA-125 (278 u/ml, <35u/ml)
- abdominal CT and pelvic examination WNL



SECOND
MRI
2 WEEKS
APART



J Dalmau, F Graus. N Engl J Med 2018;378:840-851.

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

* Data are from a review of studies.[1] ADAM denotes a disintegrin and metalloproteinase; AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 contactin-associated protein–like 2; D2R dopamine 2 receptor; DPPX dipeptidyl-peptidase–like protein 6; GABA γ-aminobutyric acid; $GABA_AR$ GABA type A receptor; $GABA_BR$ GABA type B receptor; LGI1 leucine-rich, glioma-inactivated 1; mGluR5 metabotropic glutamate receptor 5; NMDAR *N*-methyl-D-aspartate receptor; and SCLC small-cell lung cancer.

† The number of patients is the approximate number reported.

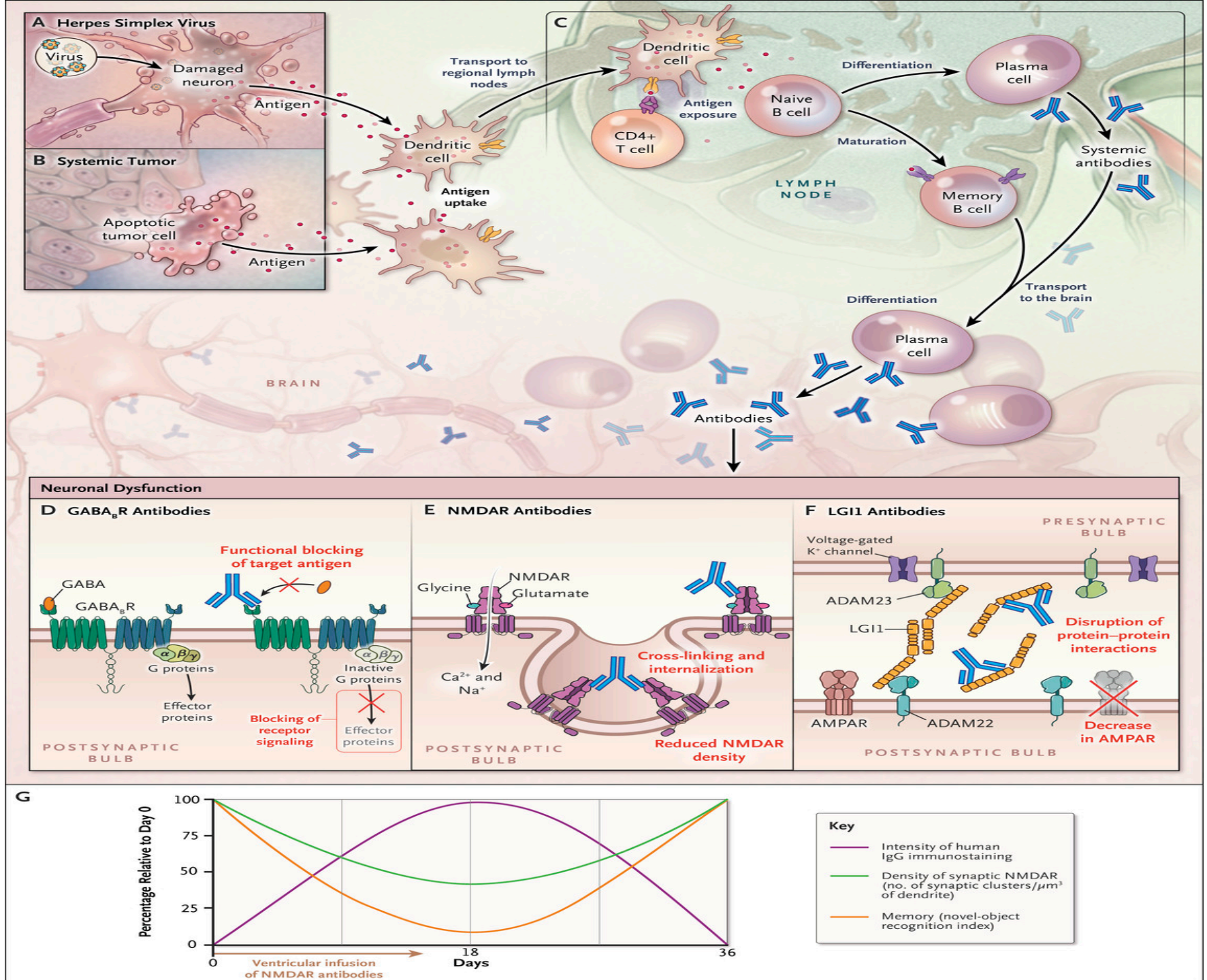
‡ Data on brain abnormalities are based on T_2-weighted MRI of the head with fluid-attenuated inversion recovery (FLAIR). Unless otherwise indicated, MRI showed normal features or nonspecific changes.

§ The association with teratoma is sex- and age-dependent. Young women frequently have an ovarian teratoma, but the presence of a tumor is uncommon in children and young men.

¶ Most patients have progressive symptoms over a period of more than 3 months.

‖ CASPR2 antibodies are frequently associated with Morvan's syndrome, a chronic disorder characterized by neuromyotonia, cognitive deterioration, sleep dysfunction (agrypnia excitata), and autonomic features.

** The frequency of an underlying tumor in patients with CASPR2 antibodies varies according to the syndrome; although patients with limbic encephalitis rarely have an underlying tumor (but if they do, the type of tumor may vary from patient to patient), 40% of patients with Morvan's syndrome have an underlying thymoma.


A Herpes Simplex Virus
Virus
Damaged neuron
Antigen
B Systemic Tumor
Apoptotic tumor cell
Antigen
Transport to regional lymph nodes
Dendritic cell
Antigen uptake
C
Dendritic cell
Antigen exposure
CD4+ T cell
Naive B cell
Differentiation
Plasma cell
Maturation
Memory B cell
LYMPH NODE
Systemic antibodies
Transport to the brain
Differentiation
Plasma cell
BRAIN
Antibodies
Neuronal Dysfunction
D GABA$_B$R Antibodies
Functional blocking of target antigen
GABA
GABA$_B$R
G proteins
Effector proteins
Inactive G proteins
Blocking of receptor signaling
Effector proteins
POSTSYNAPTIC BULB
E NMDAR Antibodies
Glycine
NMDAR
Glutamate
Ca^{2+} and Na$^+$
Cross-linking and internalization
Reduced NMDAR density
POSTSYNAPTIC BULB
F LGI1 Antibodies
PRESYNAPTIC BULB
Voltage-gated K$^+$ channel
ADAM23
LGI1
Disruption of protein–protein interactions
AMPAR
ADAM22
Decrease in AMPAR
POSTSYNAPTIC BULB
G
Percentage Relative to Day 0
100
75
50
25
0
0
18
36
Days
Ventricular infusion of NMDAR antibodies
Key
Intensity of human IgG immunostaining
Density of synaptic NMDAR (no. of synaptic clusters/μm^3 of dendrite)
Memory (novel-object recognition index)

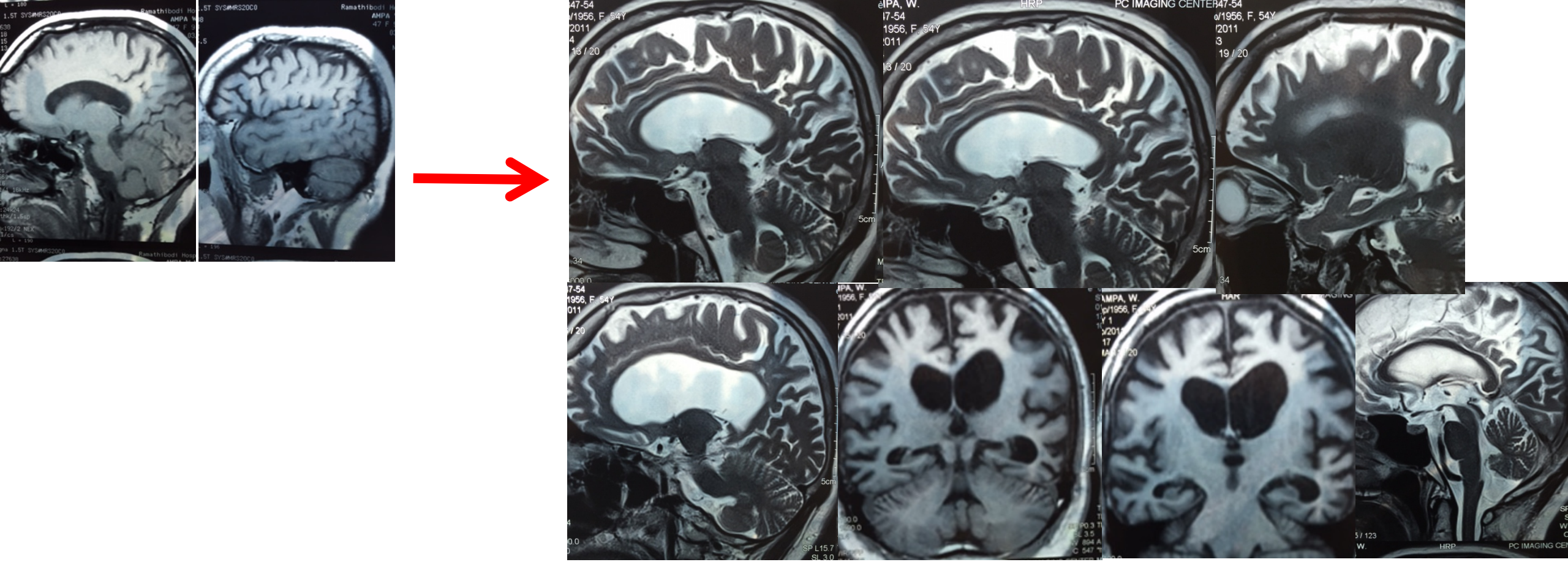
ANNA-2 (Ri) RAPID DEMENTIA NOV 2012

onset 2006 at age 50 vdo

2009 Poor memory
2010
driving X
self care X
Language X
Walking – possible

ถูกวินิจฉัยเป็นอัลไซเมอร์
ปี 2006 อายุ 50ปี

ปี 2009 ความจำแย่มาก
ปี 2010
ดูแลตนเองไม่ได้
พูดติดต่อสื่อสารไม่ได้
ได้รับอนุญาตเผยแพร่

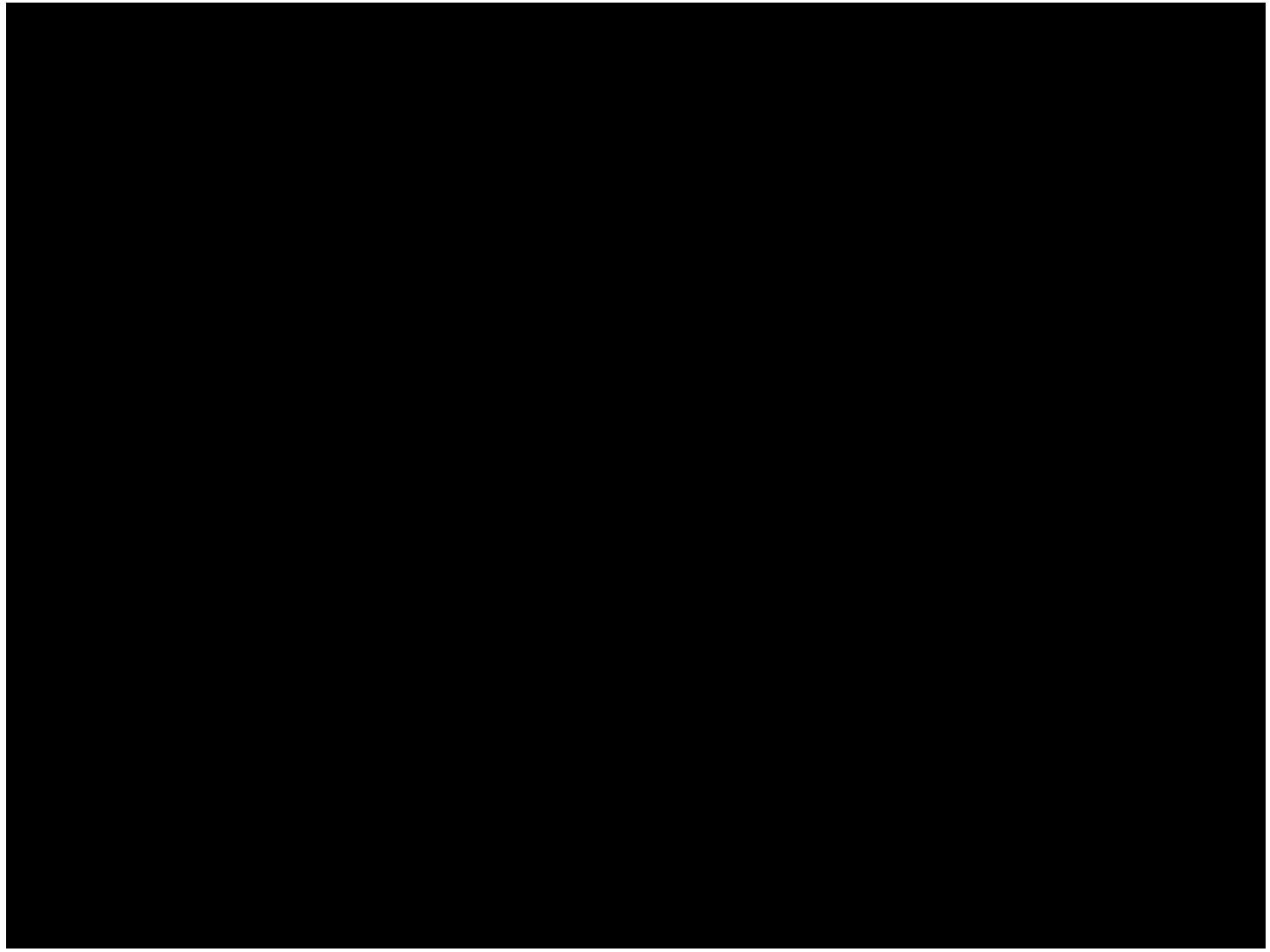


สมองเหี่ยวฝ่อรวดเร็ว ภายใน 3 ปี

ANNA-2 (Ri) RAPID DEMENTIA JAN 2013 vdo

Start IVIG
Oral prednisolone
Azathioprine

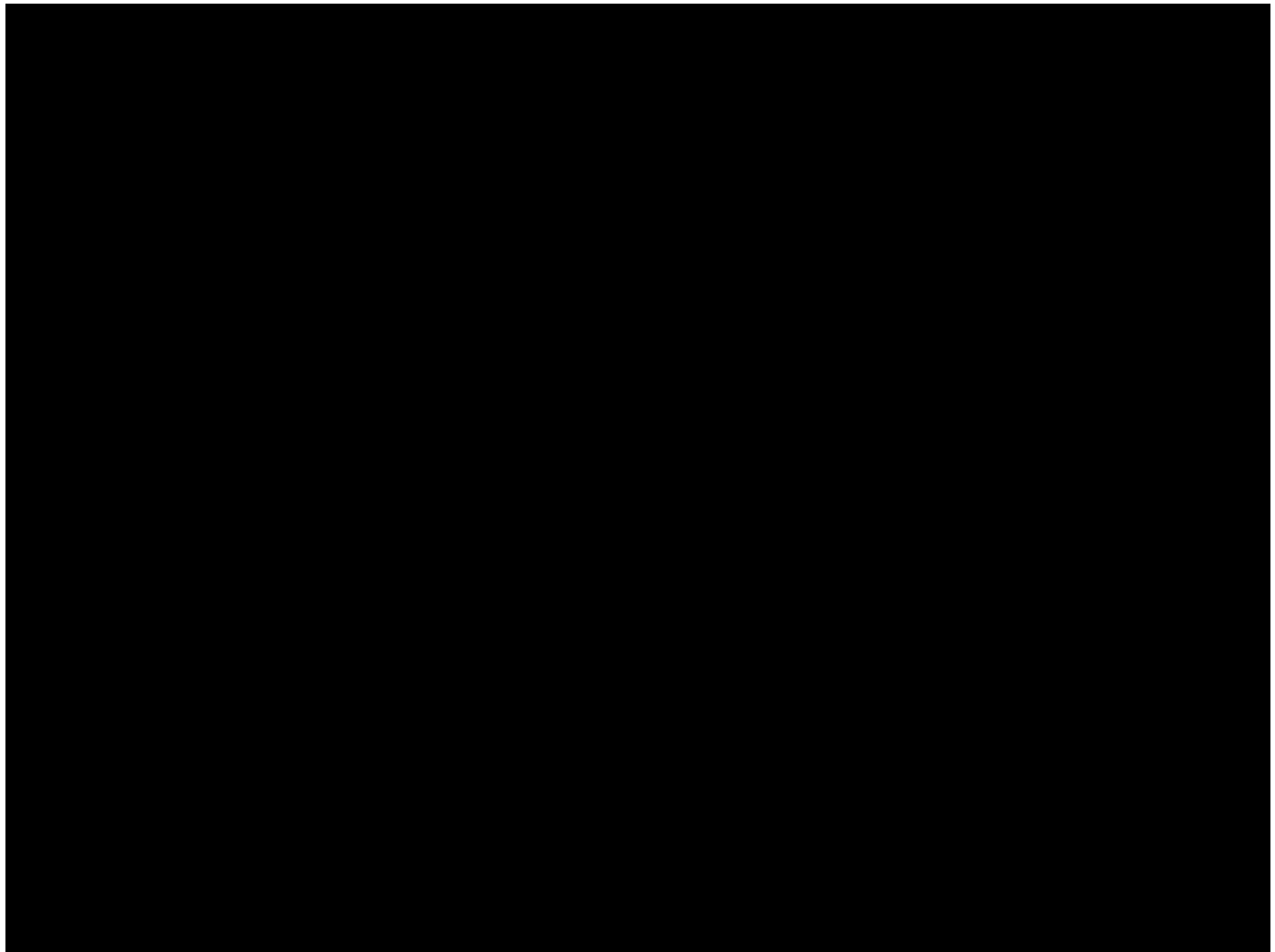
ปี **2013**
เริ่มได้รับการรักษา



ANNA-2 (Ri) RAPID DEMENTIA JAN 2015 vdo

Azathioprine

ปี **2015**
รับฟังภาษาเข้าใจ
ออกไปเที่ยว ทานอาหาร
นอกบ้านได้



INFLAMMATION

- **INFLAMMATION AS ORIGINATOR AND EXAGGERATOR OF DISEASES**

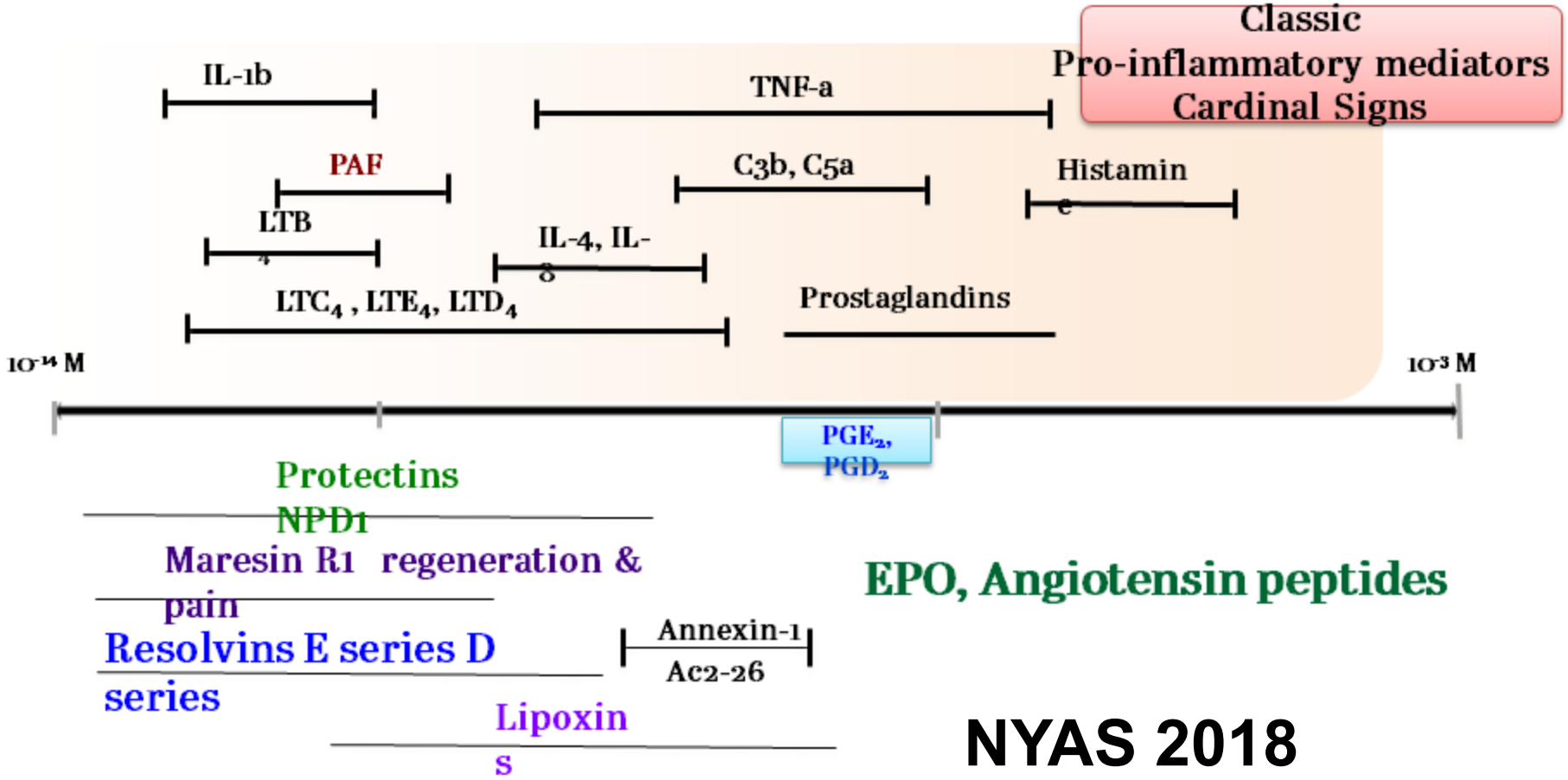
- **AUTO-INFLAMMATORY DISEASES -innate**

  http://www.nomidalliance.org/downloads.php

- **AUTOIMMUNE DISEASE-adaptive**

Chemical Mediators in Inflammation - Resolution

Lipid Mediators **Proteins, Peptides**



Anti-inflammatory,
Pro-Resolving Mediators

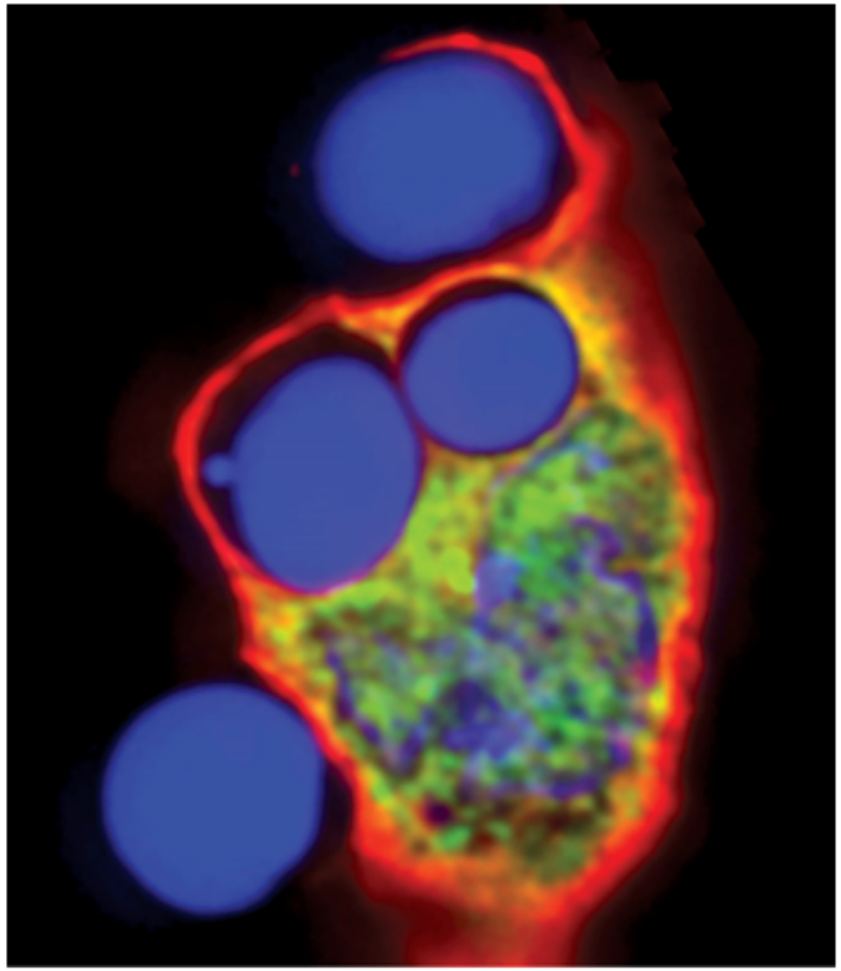
NYAS 2018
Inflammation
symposium

Endocannabinoids and phytocannabinoids

- Innate
- Adaptive

Targeting the Endocannabinoid-Specialized Pro-resolution Mediator Pathway with Lenabasum to Treat Chronic Inflammatory/Fibrotic Diseases

High-Burden Efferocytosis



- Critical to prevent necrosis *in vivo*
- Requires cell-surface membrane trafficking
- Requires handling metabolic load

npj | Aging and Mechanisms of Disease

www.nature.com/npjamd

THC

ARTICLE OPEN

Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids

Antonio Currais[1], Oswald Quehenberger[2,3], Aaron M Armando[2], Daniel Daugherty[1], Pam Maher[1] and David Schubert[1]

The beta amyloid (Aβ) and other aggregating proteins in the brain increase with age and are frequently found within neurons. The mechanistic relationship between intracellular amyloid, aging and neurodegeneration is not, however, well understood. We use a proteotoxicity model based upon the inducible expression of Aβ in a human central nervous system nerve cell line to characterize a distinct form of nerve cell death caused by intracellular Aβ. It is shown that intracellular Aβ initiates a toxic inflammatory response leading to the cell's demise. Aβ induces the expression of multiple proinflammatory genes and an increase in both arachidonic acid and eicosanoids, including prostaglandins that are neuroprotective and leukotrienes that potentiate death. Cannabinoids such as tetrahydrocannabinol stimulate the removal of intraneuronal Aβ, block the inflammatory response, and are protective. Altogether these data show that there is a complex and likely autocatalytic inflammatory response within nerve cells caused by the accumulation of intracellular Aβ, and that this early form of proteotoxicity can be blocked by the activation of cannabinoid receptors.

npj Aging and Mechanisms of Disease (2016) **2,** 16012; doi:10.1038/npjamd.2016.12; published online 23 June 2016

Biochemical Pharmacology 157 (2018) 51–66

Contents lists available at ScienceDirect

Biochemical Pharmacology

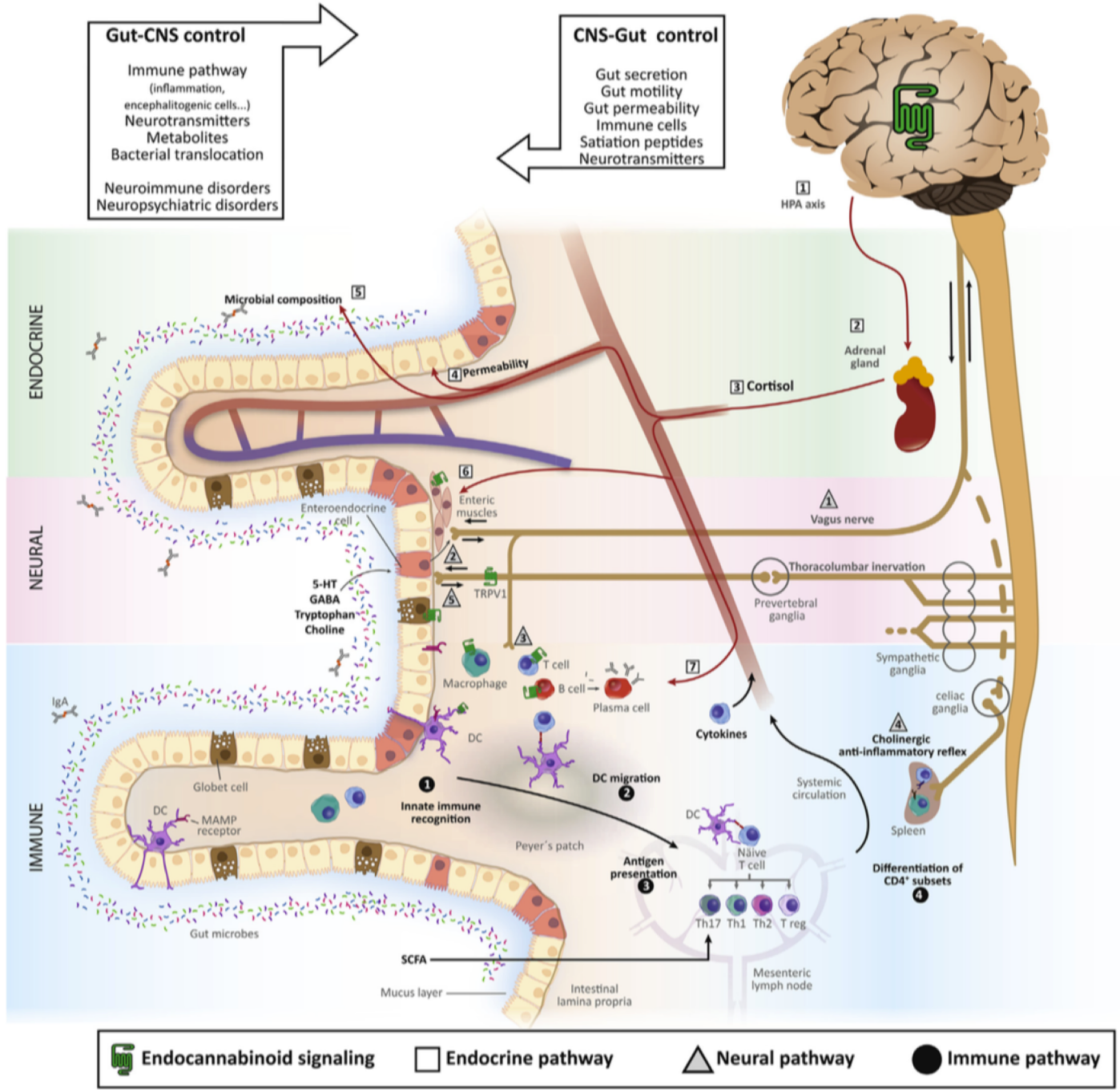
journal homepage: www.elsevier.com/locate/biochempharm

Review

Gut microbiota, cannabinoid system and neuroimmune interactions: New perspectives in multiple sclerosis

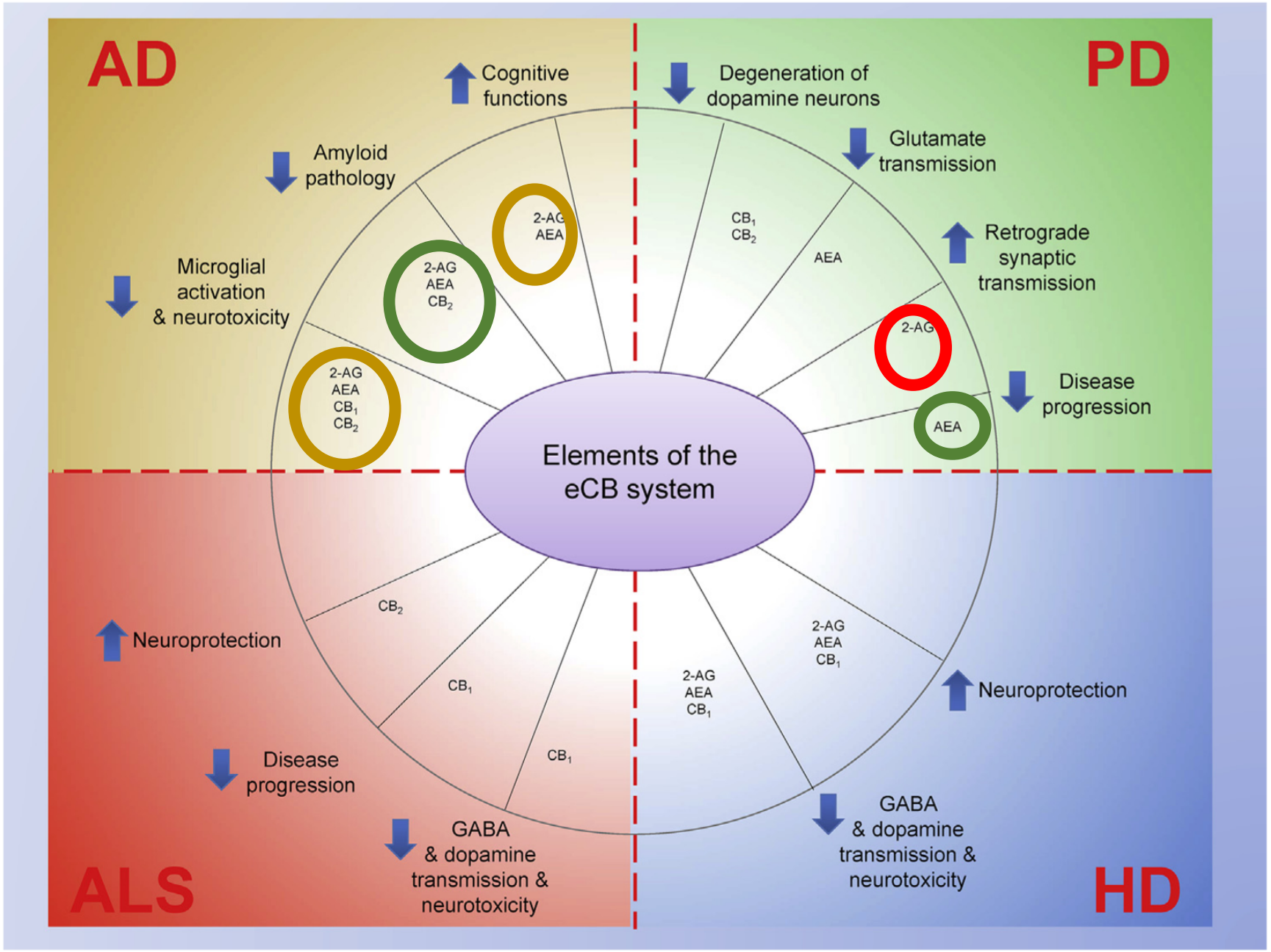
L. Mestre[a,b], F.J. Carrillo-Salinas[a,1], M. Mecha[a,b], A. Feliú[a,b], C. Guaza[a,b,*]

[a] Grupo de Neuroinmunología, Departamento de Neurobiología Funcional y de Sistemas, Instituto Cajal, CSIC, Madrid, Spain
[b] Red Española de Esclerosis Múltiple (REEM), Spain


Gut-CNS control
Immune pathway
(inflammation,
encephalitogenic cells...)
Neurotransmitters
Metabolites
Bacterial translocation
Neuroimmune disorders
Neuropsychiatric disorders
CNS-Gut control
Gut secretion
Gut motility
Gut permeability
Immune cells
Satiation peptides
Neurotransmitters
ENDOCRINE
NEURAL
IMMUNE
1 HPA axis
2 Adrenal gland
3 Cortisol
4 Permeability
5 Microbial composition
6 Enteric muscles
1 Vagus nerve
2 Thoracolumbar inervation
Prevertebral ganglia
Sympathetic ganglia
celiac ganglia
4 Cholinergic anti-inflammatory reflex
Spleen
Systemic circulation
Cytokines
7
Enteroendocrine cell
5-HT
GABA
Tryptophan
Choline
TRPV1
3
T cell
B cell
Plasma cell
Macrophage
DC
IgA
Globet cell
MAMP receptor
1 Innate immune recognition
DC migration 2
Peyer's patch
Antigen presentation 3
Naive T cell
Differentiation of CD4+ subsets 4
Th17 Th1 Th2 T reg
Gut microbes
SCFA
Mucus layer
Intestinal lamina propria
Mesenteric lymph node
Endocannabinoid signaling
Endocrine pathway
Neural pathway
Immune pathway

AEA
CB2

CBD


AD
PD
ALS
HD
Cognitive functions
Amyloid pathology
Microglial activation & neurotoxicity
Degeneration of dopamine neurons
Glutamate transmission
Retrograde synaptic transmission
Disease progression
Neuroprotection
Disease progression
GABA & dopamine transmission & neurotoxicity
Neuroprotection
GABA & dopamine transmission & neurotoxicity
Elements of the eCB system
2-AG
AEA
CB1
CB2

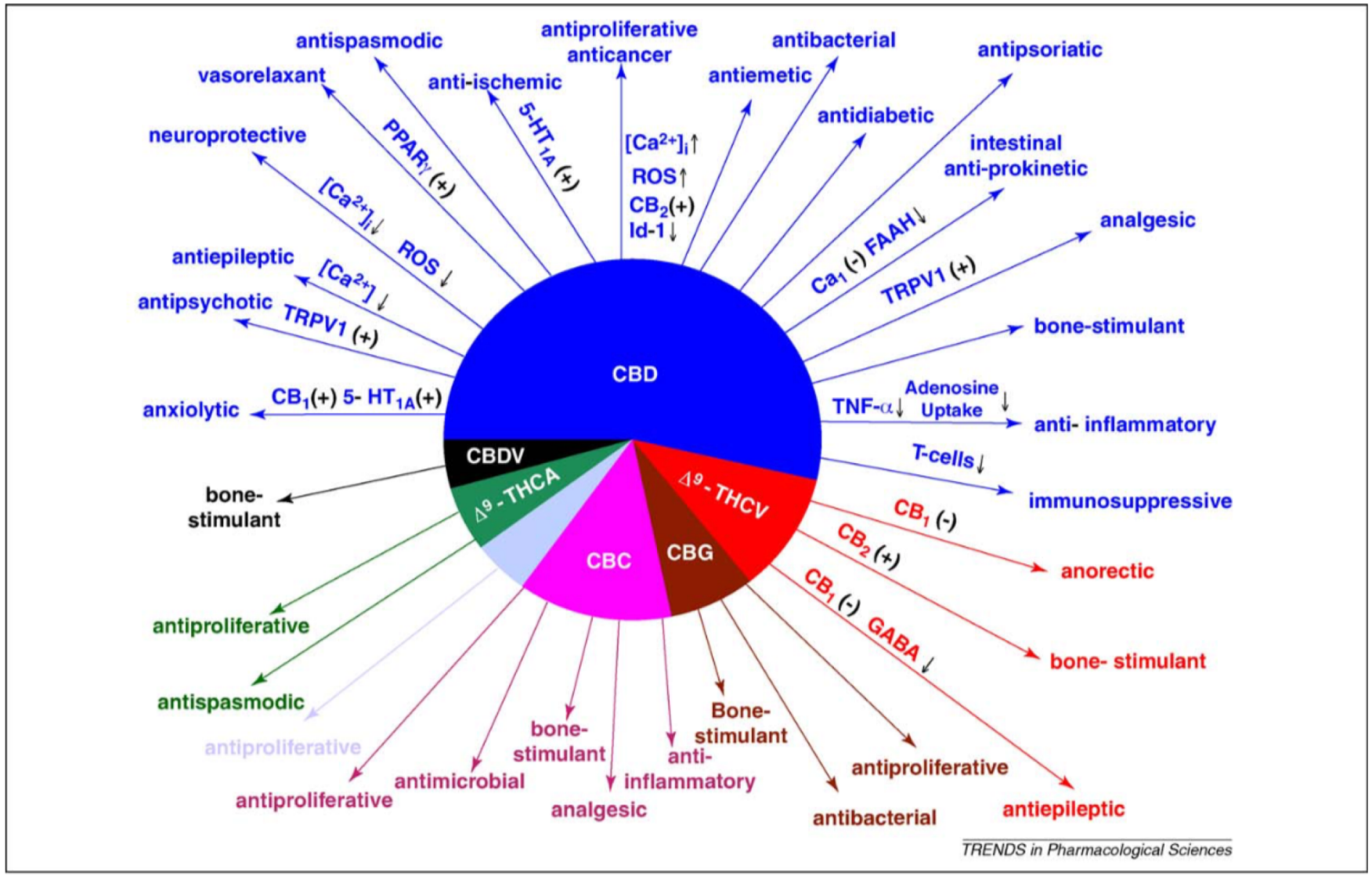


Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT_{1A}, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase.
(+), direct or indirect activation; ↑, increase; ↓, decrease.

หมอเราๆ เรื่องกัญชา

มือใหม่หัดขับ

Literature review หมอมือ **2**

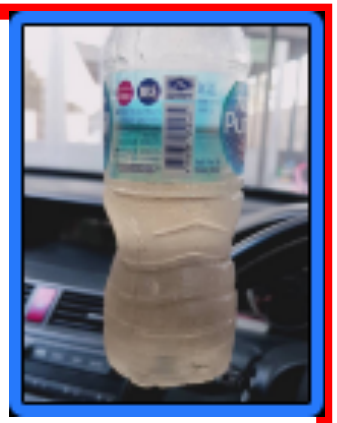
Which types of literatures to anticipate with?

How deep?

How to know what composition(s) included in each study?

Advantage of having “underground use” by implementing Thai ancient recipes

- ผู้ป่วยเป็นสมองเสื่อมอัลไซเมอร์ มาหลายปี
- ใช้ยาแผนปัจจุบัน ซึ่งเป็นยากระตุ้นให้กระฉับกระเฉงแต่ไม่ได้รักษาโรคและเร่งการทำงานของสมองซึ่งมีความผิดปกติอยู่แล้ว ให้พยามทำงานหนักขึ้นไปอีก
  แทนที่จะเป็นการใช้พลังงานอย่างมัธยัสถ์ประหยัดและสมเหตุสมผล
- ยาแผนปัจจุบันคือยากลุ่มเพิ่มสาร**acetylcholine** ในสมอง ยาที่พยายามชะลอโรค ต้าน**glutamate** ยาควบคุมอาการทางอารมณ์ ทางจิต
- ผู้ป่วยหยุดยาดังกล่าว



- ผู้ป่วยได้รับเป็นน้ำสกัดกัญชาโดยได้เล่าให้ฟังดังต่อไปนี้:
  น้องเขาให้มาเป็นดอก ต้มทานเอาก่อนครับ อาทิตย์หน้าจะสกัดเย็นทันครับ
- วันแรก:
  เมื่อวานทานไป 20 **ml.** อาการที่ดีขึ้นคือติดกระดุมเองได้ครับ จากที่ไม่ได้มาเป็นเดือนครับ
- วันที่2:
  เช้านี้ ทานอีก 100 **ml.** อารมณ์ดี ไม่ตีพ่อแล้วครับ ทดสอบบวกเลขยังไม่ได้ครับ แต่การพูดจายับยั้งชั่งใจ และไม่ด่าว่าคนอื่นเลยครับ คุณพ่อว่าเป็นสารมหัศจรรย์ครับ ขอบคุณคุณหมอและ ชายนิรนามด้วยครับ
- คุณแม่สามารถใส่เสื้อผ้าได้เองแล้วครับ หลังจากไม่สามารถใส่ได้มา 1 เดือนแล้วครับ คุณพ่อดีใจมากครับ ขอบคุณหมอมากครับ

ต่อมาเป็นแบบสกัด:

- คุณแม่ ติดกระดุมเอง ไม่ถ่ายเรี่ยราด และ ใส่เสื้อผ้าไม่กลับด้านแล้วครับ
  ทดสอบ 3+2 ยังตอบว่า 10 อยู่ครับ
  วิธีรับประทาน แบบเข้มข้น 2 หยด เช้า เย็น ใส่ในน้ำอัดลมครับ
- สรุปว่าดีขึ้นมากเลยครับ
  แต่เมื่อคืน คุณพ่องดให้ 2 หยดตอนกลางคืน โดนทุบเบาๆ ไป 2-3 ตุ๊บครับ
- อัพเดท อาการคุณแม่ครับ ประมาณ 30 วัน ครับ
  1. ติดกระดุม ใส่เสื้อไม่กลับข้าง
  2. สนทนา เรื่องเก่ากับญาติที่มาเยี่ยม พอจะถูกต้องอยู่บ้าง จาก เดิมประมาณ 10% รู้เรื่องเป็น 60% ทำให้ญาติบางคนนึกว่าไม่เป็นไร
  3. ไม่มีอารมณ์หงุดหงิด
  4. ไม่ปัสสาวะราด
  5. ความถี่ของการเดินเพ่นพ่าน ลดลง
- ยังเป็นความรู้มหาศาลที่ชมรมกัญชาสามารถเลือกชนิด สูตรได้ถูกต้อง เพราะผู้ป่วยมีอาการทางอารมณ์ทางจิตอยู่แล้วแต่การใช้กัญชาที่ถูกต้อง ช่วยอาการทางสมองได้และยังสงบอาการทางจิตได้ด้วย
- ต้องคอยติดตามต่อไปว่ายากัญชายังจะมีประสิทธิภาพอยู่ได้นานเพียงใดแต่การใช้ที่ผ่านมาหนึ่งเดือนยังไม่ต้องเพิ่มปริมาณกัญชาใดๆทั้งสิ้น

3 เดือน จากติดต่อสื่อสารไม่ได้ ช่วยตัวเองไม่ได้
กระสับกระส่าย ฉุนเฉียว VDO ได้รับอนุญาติเผยแพร่

Parkinson’s disease

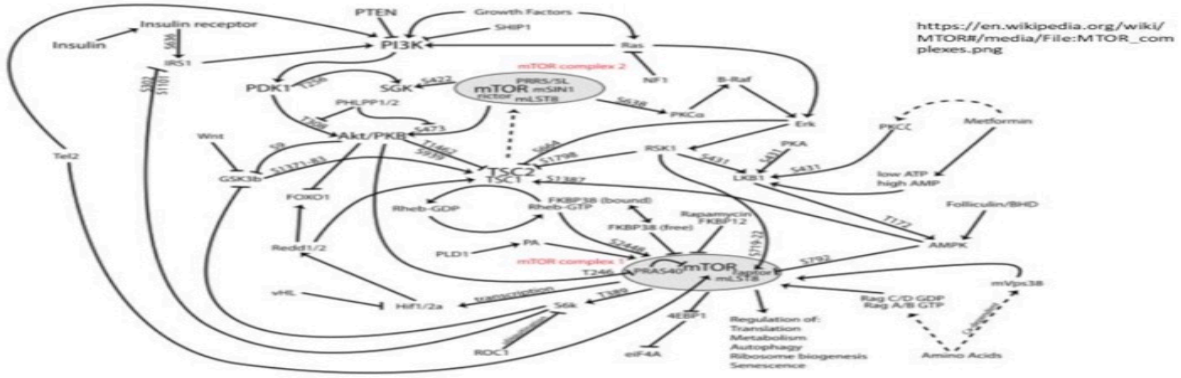
- เหลือเชื่อคืนนี้ได้ไปพบผู้ป่วยพาร์กินสันส์ซึ่งใช้ยามโหฬารและในที่สุดลูกชายก็ได้ยากัญชาจากสหรัฐใช้สองหยดเช้าสองหยดเย็นโดยที่ใช้ยาปัจจุบันน้อยมาก
  เหลือแค่ madopar 1/4 และ 3/8 เม็ด 2 เวลา
- นั่งอยู่ด้วยกัน 4 ชั่วโมงคอยสังเกตุอาการตั้งแต่ 6 โมงเย็นจนกระทั่งถึง 23.00 น.
  แทบไม่มีใครดูออกว่าเป็นพาร์กินสันส์
  การเคลื่อนไหวการทรงตัวการเดินและไม่มีการสั่นไม่มีอาการโยก
  ลดยาปัจจุบันไปได้ทั้งหมดเหลือที่กล่าวข้างต้น
  คนไข้อาการเสถียรตลอดเวลาหกเดือนที่ผ่านมา
  ราคาค่ายาที่สามารถประหยัดได้อยู่ประมาณ 20,000 ถึง 30,000 บาท
  เกรงว่าแพทย์แผนปัจจุบันต้องใจกว้าง
  กัญชาทางการแพทย์มีประโยชน์แน่

Path(s) to immortal and good health

TOR (TARGET OF RAPAMYCIN)

- TOR function dependent on nutrition status
- TOR function leads to increase in cellular protein synthesis and cell division
- too much food and obesity result in un-inhibition of TOR gene/Insulin resistance in the body and brain
- Starvation, TOR gene down-regulated to energy saving mode
- Less protein production/cell division
- Switch to autophagy mode in providing energy
- Recycling waste for energy
- TOR as stress sensor eg to oxygen insufficient/DNA damage switch off and start repairing damaged DNA

CANNABINOID SYSTEM AND LONGEVITY



CANNABIDIOL (CBD)

- **anxiolytic, anti-psychotic, antidepressant, and neuroprotective properties.**
- **CBD** acts on the ECBS as a weak **inverse agonist on CB1 receptors**, stimulates the TRVP1, and alters the hydrolysis of AEA by inhibiting fatty acid amine hydrolase.
- CBD: an **agonist of 5-HT1a serotoninergic receptors** and to regulate **stress response and compulsive behaviors.**
- CBD modulates allosterically μ and δ **opioid receptors**.
- The direct impact of CBD on glutamatergic neurotransmission is not known, but its **protective effects** on glutamate toxicity have been studied.
- Altogether, CBD has been associated with many neural circuits involved in the acquisition of addiction and subsequent drug seeking behaviors, pharmacological candidate to treat substance-use disorders.
-

Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence

Mélissa Prud'homme[1,2], Romulus Cata[1] and Didier Jutras-Aswad[1,2]

[1]Research Center, Centre hospitalier de l'Université de Montréal (CRCHUM). [2]Department of Psychiatry, Université de Montréal, Montreal, QC, Canada.

SubStance abuSe: ReSeaRch and tReatment 2015:9

ABSTRACT: Drug addiction is a chronically relapsing disorder characterized by the compulsive desire to use drugs and a loss of control over consumption. Cannabidiol (CBD), the second most abundant component of cannabis, is thought to modulate various neuronal circuits involved in drug addiction. The goal of this systematic review is to summarize the available preclinical and clinical data on the impact of CBD on addictive behaviors. MEDLINE and PubMed were searched for English and French language articles published before 2015. In all, 14 studies were found, 9 of which were conducted on animals and the remaining 5 on humans. A limited number of preclinical studies suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans. Further studies are clearly necessary to fully evaluate the potential of CBD as an intervention for addictive disorders.

KEYWORDS: review, cannabidiol, drug addiction, addictive behaviors, treatment

CITATION: Prud'homme et al. Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence. *Substance Abuse: Research and Treatment* 2015:9 33–38 doi: 10.4137/SART.S25081.

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ACADEMIC EDITOR: Gregory Stuart, Editor in Chief

TYPE: Review

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THERAPEUTIC AND PSYCHOACTIVE PROPERTIES IN CANNABIS. ECBS /*CANNABINOID RECEPTORS*/SIGNALING

CB1 CB2 THC CBD

- brain, lungs, liver, kidneys, bone, muscle, and immune system
- CB1: in the brain/PNS

addictive behavior, appetite, OBESITY, nausea, muscle spasticity, and seizures, (and throughout the body).

- Implication for Rx:

  in non-brain-diseased state-abnormal Upregulation at periphery : energy metabolism/DM-kidney

- CB2: the immune system found outside the brain in splenocytes, macrophages, monocytes, microglia, and B and T cells.

- eCBs can function as epigenetic modulators

"PERIPHERY" APPROACH BY COUNTERACTING CB1R (RE-LOCATE TO PERIPHERY IN METABOLIC DISEASE)

"CENTRAL" APPROACH SUCESSFUL BUT SUICIDE

- **eCB/ CB1R system in modulating the metabolism in several peripheral organs.**
- **eCBs, via activating the CB1R, contribute to obesity and regulate food intake.**
- **roles in modulating liver and kidney functions**
- **recently developed peripherally restricted CB1R antagonists (CBD) energy homeostasis, and in ameliorating both obesity- and diabetes-induced metabolic complications.**
- **Exception: bone remodeling and mass (CB2R agonist rather than CB1R).**

WHO FEBRUARY 2019

- ประชุมในที่ประชุมผู้เชี่ยวชาญยาเสพติด (WHO Expert Committee on Drug Dependence) ครั้งที่ 41 เมื่อพฤศจิกายน 2561
- โดยแยกระหว่างสารหลักสองสารคือ Tetrahydrocannabinoid (THC) และ Cannabidiol (CBD)
- CBD ไม่ใช่สารเสพติด มีประโยชน์
- THC มีประโยชน์ แต่เนื่องจากแฝงโทษ ถ้าใช้ผิด จึงต้องมีการควบคุม
- และได้เตรียมที่จะเรียกประชุมตัวแทนแต่ละประเทศเพื่อจะทำการโหวต กฎหมายเรื่องกัญชาฉบับแก้ไขใหม่ในเดือนมีนาคมที่จะถึงนี้

EUROPEAN PARLIAMENT FEB 13, 2019

- EU SHOULD STIMULATE INNOVATION IN MEDICAL CANNABIS
- SHOULD BE COVERD BY HEALTH INSURANCE SCHEMES
- SHOULD DISTINGUISH CLEALRY BETWEEN MEDICAL AND OTHER USES
- MEPs CALL ON MEMBER STATES TO ALLOW DOCTORS TO USE THEIR PROFESSIONAL JUDGEMENT IN PRESCRIBING
- ADDITIONAL REVENUE FOR PUBLIC AURTHORITIES, THUS, LIMITING BLACK MARKET/ENSURE QUALITY. ACCURATE LABELLING
- MENTAL DISORDERS (PSYCHOSIS, TOURETTE), EPILEPSY, ALZHEIMER'S, ARTHRITIS, ASTHMA, CNACER, CROHN'S, GLAUCOMA, OBESITY, DM, MENSTRUAL PAIN.
- ACKNOWLEDGE WHO/UN CBD AS MEDICINE

	A	B	C
1	กลุ่มยา	มูลค่าปี60* (ล้านบาท)	
2	ANTI-DEMENTIA DRUGS	2,499.00	
3	ANTI-PARKINSON DRUGS	1,230.35	
4	COX2 inhibitors	2,088.57	
5	ANTIPSYCHOTICS	1,712.50	
6	ANTIDEPRESSANTS	1,609.76	
7	รวม 5 กลุ่ม	**9,140.17**	
8			
9	* หมายถึงมูลค่าผลิตและนำเข้ายาปีพ.ศ.2560		

กลุ่มยา	มูลค่าปี60* (ล้านบาท
ANTINEOPLASTIC AGENTS	15,218.08
ENDOCRINE THERAPY	1,977.36
	17,195.43
* หมายถึงมูลค่าผลิตและนำเข้ายาปีพ.ศ.2560	

EMBRACE DIVERSITIES

- REALIZE CURRENT LIMITATION
- COST BURDEN TO PATIENTS AND NATIONAL HEALTH BUDGET
- ALTERNATIVES: LESS SIDE EFFECTS, ECONOMICAL, AFFORDBLE, ACCESSIBLE

EQUITY FOR ALL